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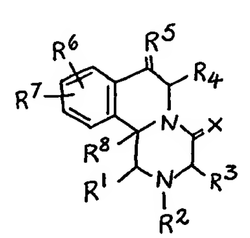
(54) RING-SUBSTITUTED PYRAZINO-ISOQUINOLINE DERIVATIVES

(71) We, MERCK PATENT GESELLSCHAFT MIT BESCHRÄNKTER HAFTUNG, of 250, Frankfurter Strasse, 61 Darmstadt, Federal Republic of Germany, a Joint-Stock Company organised under the laws of the Federal Republic of Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with new, ring - substituted 4 - oxo- and 4 - thioxo - hexahydro - 4H - pyrazino[2,1 - a]-isoquinoline derivatives and with the preparation thereof.

The new isoquinoline derivatives according to the present invention are compounds of the general formula:—



(I)

wherein R^1 is a hydrogen atom or a hydroxyl group or an alkyl radical, R^2 is a hydrogen atom or CYR^9, R^3 is a hydrogen atom or an alkyl or hydroxyalkyl radical, R^4 is a hydrogen atom or an alkyl or phenyl radical, R^5 represents two hydrogen atoms or a hydrogen atom and an alkyl or phenyl radical or a hydrogen and a halogen atom or a hydrogen atom and a hydroxyl group or represents an oxygen atom, R^6 and R^7, which may be the same or different, are hydrogen or halogen atoms or hydroxyl, amino, nitro or cyano groups or alkyl, alkoxy, acyloxy, monoalkylamino, dialkylamino or acylamino radicals or the group Z, R^8 is a hydrogen atom or an alkyl radical, R^9 is a hydrogen atom or an alkyl radical containing up to 6 carbon atoms or a cycloalkyl or cycloalkenyl radical containing 5 to 7 carbon atoms and is either unsubstituted or is substituted by oxygen or is substituted once or twice by R^{10} and/or is interrupted in the ring by oxygen, sulphur, SO or SO_2, or is a phenyl radical which is either unsubstituted or substituted once or twice by R^{10} or Z, or is a thienyl, pyridyl or phenoxy radical or is R^{11}, R^{10} is a fluorine or chlorine atom or a hydroxyl, nitro or amino group or a monoalkylamino, dialkylamino or acylamino radical, R^{11} is an alkoxy radical or a cycloalkoxy radical containing 5 to 7 carbon atoms, X and Y, which can be the same or different, are oxygen or sulphur atoms and Z is a phenylazo or naphthylazo radical which is either unsubstituted or is substituted by halogen, hydroxyl, amino, alkyl, alkoxy, monoalkylamino, dialkylamino, COOH and/or SO_3H; and wherein the alkyl, hydroxyalkyl, alkoxy and acyl radicals contain up to 4 carbon atoms insofar as they are not otherwise defined and wherein R^2 is CSR^9 or COR^{11} when R^1 and R^3 to R^8 are all hydrogen atoms and X is an oxygen atom; and the physiologically compatible salts thereof.

We have found that the new compounds of general formula (I) have a good compatability and possess valuable parasitological and pharmaceutical properties. Thus, they are,

inter alia, valuable anthelmintics and display, in particular, a broad spectrum of activity against cestodes and trematodes. Furthermore, some of the new compounds have an action upon the central nervous system and, in particular have psyschotropic, as well as blood pressure-influencing and especially blood pressure-lowering properties.

In addition, some of the new compounds have tranquilising, adrenolytic and muscle-relaxing properties, which can be ascertained by conventional methods known for this purpose. These activities have been determined, for example, on mice, rats and rhesus monkeys.

Therefore, the new compounds of general formula (I) and the physiologically compatible salts thereof can be used as pharmaceuticals in human and/or veterinary medicine, especially for achieving anthelmintic actions, and also as intermediates for the preparation of other pharmaceuticals.

The alkyl, hydroxyalkyl, alkoxy and acyl groups given in the definitions of the symbols R^1 to R^{11} and Z can each contain up to 4 carbon atoms, insofar as nothing is stated to the contrary. Preferably, however, these radicals contain 1 or 2 carbon atoms. Consequently, alkyl preferably signifies methyl, but also ethyl and, of lesser importance, *n* - propyl, isopropyl, *n* - butyl, isobutyl, *sec.* - butyl or *tert.* - butyl. Hydroxyalkyl means, in the first place, hydroxymethyl or 2 - hydroxyethyl. Alkoxy means, in the first place, methoxy, as well as ethoxy but also *n* - propoxy, isopropoxy, *n* - butoxy, isobutoxy, *sec.* - butoxy or *tert.* - butoxy. Acyl is preferably acetyl but can also be formyl, propionyl, *n* - butyryl or isobutyryl. The same also applies to the groups derived from these radicals. Thus, monoalkylamino is preferably methylamino, dialkylamino is preferably dimethylamino or diethylamino, acylamino is preferably acetylamino and acyloxy is preferably acetoxy.

In the substituent R^9, the alkyl radical can contain up to 6 carbon atoms and, in addition to the above-mentioned meanings, can also stand, for example, for straight-chained or branched pentyl or hexyl radicals.

In detail, the symbol R^1 preferably means a hydrogen atom or a hydroxyl group or a methyl radical. The symbol R^2 is preferably CYR^9 but the compounds in which R^2 is a hydrogen atom are also of importance. The symbol R^3 is preferably a hydrogen atom or a methyl or 2 - hydroxyethyl radical. The symbol R^4 is preferably a hydrogen atom or a methyl radical. The symbol R^5 preferably stands for two hydrogen atoms or for one hydrogen atom and a methyl radical. At least one of the symbols R^6 and R^7 is preferably a hydrogen atom. Furthermore, these symbols also preferably stand for fluorine, chlorine or bromine atoms, or for hydroxyl, amino or nitro groups or methyl or methoxy radicals. The symbol R^8 preferably stands for a hydrogen atom or for a methyl radical.

The symbol R^9 preferably stands for an unsubstituted or substituted cycloalkyl radical containing 5 or 6 carbon atoms and especially for an unsubstituted or substituted cyclohexyl radical, as well as for an unsubstituted or substituted phenyl radical. Especially preferred substituents of the cycloalkyl radical are oxygen (for example in the form of a keto group), fluorine atoms, nitro and amino groups and methylamino, dimethylamino or acetylamino radicals but also chlorine atoms or ethylamino, diethylamino, formylamino and propionylamino radicals. Preferred substituents of the phenyl radical are fluorine atoms or amino or nitro groups or methylamino, dimethylamino, formylamino or acetylamino radicals which are preferably in the *m*- or *p*-position but can also be in the *o*-position. Further substituents of the phenyl radical can be, for example, chlorine atoms, hydroxyl groups or ethylamino, diethylamino, *n* - propylamino, propionylamino, *n* - butyrylamino and isobutyrylamino radicals which again are preferably in the *m*- or *p*-position but can also be in the *o*-position. The symbol R^9 also preferably stands for a 2- or 3 - cyclohexenyl radical, a thienyl radical connected in the 2- or 3-position, a pyridyl radical connected in the 2-, 3- or 4-position, a tetrahydropyranyl radical connected in the 2-, 3- or 4-position, a thiacyclohexyl radical connected in the 2-, 3- or 4-position, which can be substituted once or twice on the sulphur atom by oxygen (but especially thiacyclohexyl - 4), a cyclohexadienyl radical or R^{11}. The symbol R^9 can also signify, for example, an alkyl radical containing up to 6 carbon atoms or a cyclopentyl, cycloheptyl, 2- or 3 - cyclopentenyl or 2-, 3- or 4 - cycloheptenyl.

The symbol R^{10} preferably stands for a fluorine atom or an amino group or a methylamino, dimethylamino, formylamino, acetylamino or nitro radical. The symbol R^{11} preferably stands for a methoxy or cyclohexyloxy radical. The symbol Z preferably means, in particular, a 4 - hydroxyphenylazo, 4 - methoxyphenylazo, 4 - aminophenylazo, 4 - methylaminophenylazo or 4 - dimethylaminophenylazo radical or a naphthyl - 1 - azo or naphthyl - 2 - azo radical, which can be substituted in the 1- or 2-, 4-, 6-, 7-, 8- or 9-position by hydroxyl, alkoxy, amino, alkylamino, dialkylamino, COOH or SO_3H.

Consequently, preferred compounds according to the present invention are, in particular, those of general formula (I) in which at least one of the symbols has one of the above-given preferred definitions. Some of these preferred groups of compounds can be defined by the following part formulae I*a* to Is, which correspond to the above-given general formula (I) and wherein the symbols not more

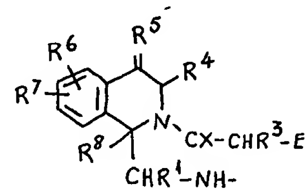
specifically identified have the meanings given in general formula (I):

in *Ia* R^1 is hydrogen;
in *Ib* R^2 is hydrogen;
in *Ic* R^2 is COR^9;
in *Id* R^2 is CS - alkyl, CS - cycloalkyl containing 5 or 6 carbon atoms or thiobenzoyl;
in *Ie* R^3 is hydrogen;
in *If* R^4 is hydrogen or methyl;
in *Ig* R^5 represents two hydrogen atoms or a hydrogen atom and a methyl radical;
in *Ih* R^6 and R^7 are hydrogen;
in *Ii* R^8 is hydrogen;
in *Ij* R^1, R^3, R^6 to R^8 are hydrogen;
in *Ik* R^1 and R^3 to R^8 are hydrogen and X is sulphur;
in *Il* R^2 is COR^9, R^9 being alkyl containing up to 4 carbon atoms, cyclohexyl which is either unsubstituted or is substituted by oxygen, one or two fluorine atoms, methylamino or dimethylamino, or phenyl which is either unsubstituted or substituted in the *m*- or *p*-position by fluorine, amino, methylamino or dimethylamino, or tetrahydropyranyl or thiacyclohexyl connected in the 2- or 4-position;
in *Im* R^2 is COR^9, R^4 is methyl and R^9 is phenyl, cyclohexyl, tetrahydropyranyl or thiacyclohexyl;
in *In* R^2 is COR^9, R^5 is methyl and R^9 is phenyl, cyclohexyl, tetrahydropyranyl or thiacyclohexyl;
in *Io* R^2 is COR^9, R^4 or R^5 is methyl and R^9 is a phenyl or cyclohexyl radical substituted by nitro, amino or fluorine in the 2- or 4-position;
in *Ip* R^1 is hydrogen or hydroxy, R^2 is CYR^9, R^3 is hydrogen, methyl or 2 - hydroxyethyl, R^4 is hydrogen or methyl, R^5 represents two hydrogen atoms or a hydrogen atom and a methyl radical, one of the symbols R^6 and R^7 is hydrogen, hydroxyl or methoxy and the other is hydrogen, hydroxyl, amino, nitro, chlorine, methyl or methoxy, R^8 is hydrogen, R^9 is alkyl containing up to 3 carbon atoms, cyclohexyl, oxocyclohexyl, tetrahydropyranyl, thiacyclohexyl, phenyl, fluorophenyl, aminophenyl, nitrophenyl, pyridyl, ethoxy, cyclohexyloxy or phenoxy and X and Y, which can be the same or different, are oxygen or sulphur atoms;
in *Iq* R^1 is hydrogen, R^2 is CYR^9, R^3 is hydrogen or methyl, R^4 is hydrogen or methyl, R^5 signifies two hydrogen atoms or a hydrogen atom and a methyl radical, one of the symbols R^6 and R^7 stands for hydrogen and the other for hydrogen, amino, nitro or chlorine, R^8 is hydrogen, R^9 is alkyl containing up to 3 carbon atoms, cyclohexyl, phenyl, fluorophenyl, aminophenyl, nitrophenyl or pyridyl and X and Y, which can be the same or different, are oxygen or sulphur atoms;
in *Ir* R^1 is methyl; and
in *Is* R^2 is thiacyclohexyl - 4 - carbonyl.

The present invention also provides a process for the preparation of compounds of general formula (I) as well as of the physiologically compatible salts thereof, wherein a compound of the general formula:—

$$Q—R^2 \qquad (II)$$

wherein Q is a radical of one of the following general formulae:—



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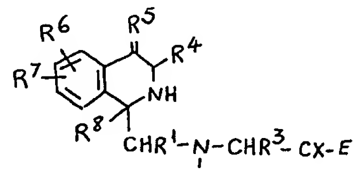

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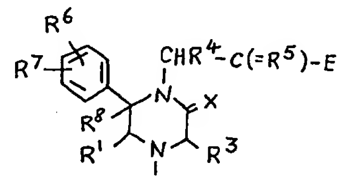
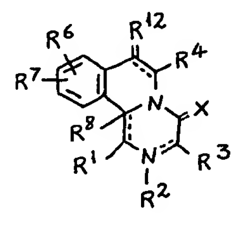


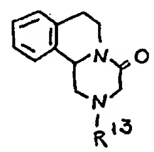
E is a halogen atom, a hydroxyl group or a functionally changed hydroxyl group and R^1 to R^8 and X have the same meanings as in general formula (I), is cyclised under conditions splitting off HE; or a compound of the general formula:—



(III)

wherein R^{12} has the same meaning as R^5 or is an alkylidene radical containing up to 4 carbon atoms and the symbols R^1 to R^8 and X have the same meanings as in general formula (I) and the dotted lines indicate that in these places there can be at least one double bond, with the proviso that R^{12} is an alkylidene radical when there is no double bond at any of these positions, or a salt of

said compound, is treated with a reducing agent; or a compound of the general formula:—



(IV)

wherein R^{13} is a hydrogen atom or COR^{14}, R^{14} is a hydrogen atom, an alkyl radical containing up to 6 carbon atoms or a cycloalkyl or cycloalkenyl radical containing 5 to 7 carbon atoms which is either unsubstituted or is substituted by oxygen or once or twice by R^{10} and/or interrupted in the ring by oxygen, sulphur, SO or SO_2 or is a phenyl radical which is either unsubstituted or is substituted once or twice by R^{10} or Z or is a thienyl or pyridyl radical and R^{10} and Z have the same meanings as in general formula (I), is treated with a hydroxylating, hydroxyalkylating, halogenating or nitrating agent or with an agent giving off sulphur; or a compound of general formula (IV), wherein R^{13} is a hydrogen atom, is treated with a thioacylating agent or with a compound of the general formula

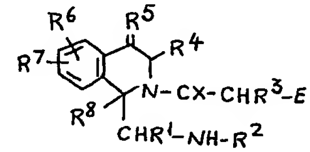
$$R^{11}—CO—E,$$

wherein R^{11} and E have the above given meanings; and, if desired, in the product obtained, one or more of the radicals R^1 to R^8 and X are converted into one or more different radicals R^1 to R^8 and X and/or when the product obtained is a racemic compound, this is resolved into its optical antipodes and/or a compound obtained of general formula (I) is converted into a physiologically compatible salt with an acid or a base or into a quaternary ammonium salt and/or a base of general formula (I) is liberated from an acid-addition salt thereof.

Otherwise, the above-described preparation of the compounds of general formula (I) takes place in known manner by known methods such as are described in the literature (for example in standard reference works, such as Houben-Weyl, Methoden der organischen Chemie, pub. Georg Thieme Verlag, Stuttgart), namely, under the reaction conditions which are known and are suitable for the said reactions.

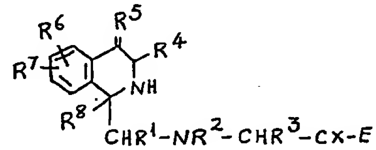
If desired, the starting materials used for the preparation of the compounds of general formula (I) can be formed *in situ* in such a manner that they are not isolated from the reaction mixture but are immediately further reacted to give the desired compounds (I).

More particularly, for the preparation of compounds of general formula (I) by cyclisation, there can be used compounds of the following general formulae:



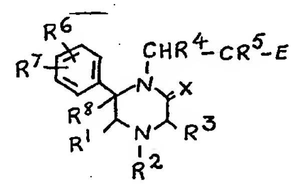
(II*a*)

or



(II*b*)

or



(II*c*)

wherein R^1 to R^8, X and E have the above-given meanings. The tetrahydroisoquinoline derivatives (II*a*) and (II*b*) are preferably used for the cyclisation.

In general formulae (II), (II*a*), (II*b*) and (II*c*), the symbol E stands for a group which is eliminated by the reaction. Therefore, the nature of this substituent is not critical. E is preferably a chlorine or bromine atom or a hydroxyl group; furthermore, as well as being a fluorine or iodine atom, E can also be an esterified hydroxyl group, especially a reactively esterified hydroxyl group, for example, an alkylsulphonyloxy radical with preferably up to 6 carbon atoms, such as a methanesulphonyloxy radical, an arylsulphonyloxy radical with preferably 6 to 10 carbon atoms, such as a benzenesulphonyloxy, *p* - toluene - sulphonyloxy or 1- or 2 - naphthalene - sulphonyloxy radical, or also an acyloxy radical, especially an alkanoyloxy radical with preferably up to 7 carbon atoms, such as an acetoxy or heptanoyloxy radical, or a benzoyloxy radical, as well as an ether group which can easily be split off, such as a tetrahydropyranyl - 2 - oxy radical, or, if this radical is part of an ester (formula (II*b*) or formula (II*c*), if R^5 is oxygen), can also be an alkoxy radical with preferably up to 4 carbon atoms, especially a methoxy or ethoxy radical.

More particularly, E in compounds of general formula (II*a*) is preferably a chlorine, bromine or iodine atom or one of the above-mentioned sulphonic acid ester radicals, especially a *p* - toluene - sulphonyloxy radical. In compounds of general formula (II*b*), E is preferably a hydroxyl group or an alkoxy or

acyloxy radical containing up to 4 carbon atoms or a halogen atom. In compounds of general f rmula (II*c*), E is preferably a hydroxyl group or a halogen atom.

The compounds of general formula (II) are cyclised in the presence or absence of a catalyst and preferably of a basic or acidic catalyst, as well as in the presence or absence of an additional inert solvent, at a temperature of from about −20 to +300°C.

The choice of the catalysts to be employed depends essentially upon the constitution of the starting material and of the compound HE to be split off. More particularly, as bases there can be used, for example, alkali metal or alkaline earth metal hydroxides, such as sodium, potassium, barium or calcium hydroxides, alkali metal or alkaline earth metal carbonates, such as sodium or potassium carbonates, alkali metal or alkaline earth metal bicarbonates, such as sodium or potassium bicarbonate, alkali metal or alkaline earth metal hydrides, such as sodium or potassium hydride, alkali metal or alkaline earth metal amides, such as sodamide, potassamide or lithium, sodium or potassium piperidide or di-isopropylamide, or alkali metal or alkaline earth metal alcoholates, such as sodium or potassium methylate, sodium or potassium ethylate or potassium *tert.* - butylate, organo - alkali metal compounds, such as butyl lithium, phenyl lithium, or naphthyl sodium, as well as the alkali metal salts of weak acids, such as sodium acetate, and also ammonia and primary, secondary and, in particular, tertiary amines, such as triethylamine, dimethylaniline or pyridine, and quaternary bases, such as benzyl trimethyl ammonium hydroxide. As acids, there can be used, for example, hydrohalic acids, such as hydrofluoric, hydrochloric or hydrobromic acid, sulphuric acid, phosphoric acid or polyphosphoric acid, as well as Lewis acids, such as aluminium trichloride, aluminium tribromide, boron trifluoride, zinc chloride, tin tetrachloride, gallium trichloride or gallium tribromide, and also inorganic acid halides, such as phosphorus trichloride, phosphorus pentachloride, thionyl chloride or phosphorus oxychloride, or agents splitting off water, for example carbodiimides, such as dicyclohexyl carbodiimide. The above-mentioned acids and Lewis acids are especially useful for the cyclisation of compounds of general formula (II*c*), which takes place according to the methods used for Friedel-Crafts alkylation or acylation.

As inert solvents, there can be used, for the cyclisation of compounds of general formulae (II*a*) and (II*b*), especially alcohols, such as methanol, ethanol, isopropanol, *n* - butanol or *tert.* - butanol; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran or dioxan; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether (methyl glycol or ethyl glycol), ethylene glycol dimethyl ether (diglyme); ketones, such as acetone; amides, such as dimethylformamide or hexamethyl - phosphoric acid triamide; nitriles, such as acetonitrile; nitro compounds, such as nitromethane or nitrobenzene; sulphoxides, such as dimethyl sulphoxide; carbon disulphide; tertiary bases, such as pyridine; chlorinated hydrocarbons, such as methylene chloride, chloroform or trichloroethylene; hydrocarbons, such as petroleum ether, hexane, benzene, toluene or xylenes. There can also be used mixtures of water with one of the above-mentioned alcohols, for example 60% ethanol, as well as mixtures of water with acetone or dioxan. For the cyclisation of compounds of general formula (II*c*), it is preferred to use the solvents which are typical for Friedel-Crafts alkylations and acylations, such as petroleum ether, hexane, nitrobenzene or carbon disulphide. These compounds can also be cyclised by the action of tertiary amines in high boiling alcohols, such as cyclohexanol.

More particularly, the compounds of general formula (II*a*) are preferably cyclised in the presence of strong bases, such as butyl lithium or potassium *tert.* - butylate, in polar solvents, such as tetrahydrofuran, dimethylformamide, hexamethyl phosphoric acid triamide or *tert.* - butanol, at temperatures of from about −20°C. to +200°C., reaction times of from about 15 minutes to about 30 hours thereby usually being necessary. The cyclisation of compounds of general formula (II*b*) takes place especially advantageously, in the absence of a solvent, by heating to temperatures of from about 140 to 250°C. and preferably of from 170 to 210°C., whereby it is possible to work at atmospheric pressure or also under reduced pressure. As catalysts for the cyclisation of compounds of general formula (II*c*), it is preferred to use hydrofluoric acid or aluminium trichloride, whereby there can be employed either an excess of the cyclisation agent, such as hydrofluoric acid, as solvent or there can also be employed one of the above-mentioned additional inert solvents. Compounds of general formula (II*c*) are preferably cyclised at a temperature of from about 0 to 150°C. and especially at a temperature of from 20 to 80°C.

It is also possible to cyclise a compound of general formula (II) (E=OH) by first reacting it with, for example, thionyl chloride, optionally in the presence of a base, such as triethylamine or pyridine, to give the corresponding chloride of general formula (II) (E=Cl) which is then allowed to react further *in situ* to give a compound of general formula (I).

The hexahydro - pyrazino - isoquinoline derivatives of general formula (I) can also be obtained by reduction of compounds of general formula (III), preferably at a tem-

perature of from about −80 to +250°C., in the presence of at least one inert solvent.

The compounds of general formula (III) correspond to those of general formula (I) except that, in addition, they contain in the 11*b*(1)- and/or 2(3)- and/or 6(7)-position, an additional double bond and/or instead of the radical R^5, in the 7-position there is present an alkylidene group containing up to 4 carbon atoms and preferably a methylene or ethylidene group. If an additional double bond is present in the 2(3)-position, then either radical R^2 is absent from compounds (III) or the compounds (III) are present in the form of a quaternary salt. Of the starting materials of general formula (III), those are preferred with a double bond in the 11*b*(1)-position.

Catalytic hydrogenation is preferably used for the reduction. As catalysts for the hydrogenation, there can be used, for example, noble metals or nickel or cobalt catalysts, as well as mixed catalysts, such as copper-chromium oxide. As noble metals, there are preferably used platinum or palladium, which can be present on carriers, such as charcoal, calcium carbonate or strontium carbonate, or as oxides or in finely-divided form. Nickel and cobalt catalysts are preferably employed as Raney metals. It is also possible to use complex compounds of heavy metals as catalysts, for example, soluble rhodium complexes, such as hydridocarbonyl - tris - (triphenyl - phosphine) rhodium. The hydrogenation can be carried out at pressures of from about 1 to 200 ats. and at temperatures of from about −80 to +200°C. and preferably at temperatures of from 20 to 100°C. The reaction can be carried out in an acidic, neutral or basic medium, preferably in the presence of one of the inert solvents already mentioned above or also in the presence of carboxylic acids, such as acetic acid, or of esters, such as ethyl acetate. The hydrogenation is preferably carried out on Raney nickel or with one of the above-mentioned platinum or palladium catalysts in an alcohol, such as methanol or ethanol, at ambient temperature and atmospheric pressure.

If, in the course of the reaction, new asymmetric centres arise, for example of the $C_{(11b)}$ atom, the reduction can also be directed in such a manner that one of the two possible antipodes of the compounds of general formula (I) is formed exclusively or at least to a preponderant extent. This can take place, for example, by asymmetric hydrogenation in which, as catalysts, there can be used, for example, Raney nickel, which is to be previously treated with an asymmetrical modifying reagent, for example, with a solution of an optically-active hydroxy or amino acid, such as tartaric acid, citric acid, alanine, isoleucine, lysine, phenylalanine, valine or leucine. Furthermore, as catalyst for an asymmetric hydrogenation in the heterogeneous phase, there can be used a heavy metal catalyst which is applied to a natural or synthetic polymer, for example palladium or platinum on silk or on a specially prepared silica gel or polyamino acid carrier, such as are described in the literature. In homogeneous phase, asymmetric hydrogenation can take place, for example, with the use of a soluble rhodium complex. The asymmetric hydrogenation is carried out under the above-given conditions, preferably at 1—3 ats. pressure and at a temperature of from about 20 to 50°C.

The compounds of general formula (I) can also be obtained from compounds of general formula (IV) by hydroxylation, hydroxalkylation, halogenation or nitration or by treatment with an agent giving off sulphur.

Hydroxylation of compounds of general formula (IV) can take place, for example, in the 1-position by treating the starting material with hydrogen peroxide or with a derivative thereof, such as performic acid, peracetic acid, perbenzoic acid or 3 - chloroperbenzoic acid. It is preferable to operate in an inert solvent, especially in methylene chloride, chloroform or diethyl ether, at a temperature of from 0 to 50°C. and more preferably from 20 to 30°C. The reaction is finished under these conditions after about 1 to 48 hours. It proceeds especially well with starting materials of general formula (IV) in which R^{13} is a pyridyl - carbonyl radical.

A hydroxyalkyl radical can be introduced into the 3-position of compounds of general formula (IV) by hydroxyalkylation. As hydroxyalkylation agent, there is preferably used an alkylene oxide or a haloalcohol containing up to 4 carbon atoms, for example ethylene oxide or 2 - bromoethanol. The hydroxalkylation is, as a rule, carried out in an inert solvent, preferably in liquid ammonia and/or an ether, such as diethyl ether, tetrahydrofuran or dioxan, a strong base preferably being added as catalyst, especially sodamide, potassamide or lithamide, lithium diisopropylamide or butyl lithium. The reaction temperature is from about −80 to +30°C. The reaction is finished after about 1 to 48 hours.

Furthermore, it is possible, by halogenation, to introduce one or more halogen atoms, preferably chloride or bromine atoms, into compounds of general formula (IV). Thus, it is possible to react compounds (IV) with elementary chlorine or bromine in an inert solvent, such as diethyl ether, carbon tetrachloride or acetic acid, using, as catalysts, for example, iron filings, iodine, ferric chloride or aluminium chloride. The reaction temperatures are preferably of from about −30 to +100°C. According to the methods described in the literature, the conditions can be so selected that the halogenation takes place preferentially in the aromatic nucleus or in the 7-position. In the aromatic nucleus, the 8- and 11-positions are preferably substituted. It is also possible that several halogenation pro-

ducts are formed simultaneously; these can be separated, for example, by chromatography or by crystallisation. Halogenation is also possible with other halogenating reagents, for example, with acyl hypohalides or N - halo - imides, such as N - chloro- or N - bromosuccinimide, in which case, as a rule, the reaction is carried out in an inert solvent in the given temperature range.

By treatment with nitrating agents, one or more nitro groups can be introduced into the molecule of the starting compounds of general formula (IV). Substitution preferably takes place in the 8- or 11-position. As nitrating agent, there is preferably used nitric acid or a derivative thereof, for example, a salt, ester, halide or anhydride (i.e. a nitrogen oxide). The nitration is advantageous carried out in the presence of an acidic catalyst, for example, sulphuric acid, as well as hydrofluoric acid or a Friedel-Crafts catalyst, such as boron trifluoride, aluminium trichloride or ferric chloride. An excess of the nitrating agent, for example of nitric acid, and/or an excess of the catalyst, for example sulphuric acid, can simultaneously serve as solvent. However, it is also possible to carry out the nitration in the presence of one or more additional inert solvents. As inert solvent, it is preferred to use acetic acid. It can also be advantageous to operate in a two-phase system by using a chlorinated hydrocarbon, such as methylene chloride, chloroform or carbon tetrachloride as solvent. As a rule, the nitration is carried out at a temperature of from -20 to $+50$°C. and preferably of from 0 to 20°C.

By treatment of the compounds of general formula (IV) with an agent giving off sulphur, preferably with phosphorus pentasulphide, the carbonyl groups can be converted into thiocarbonyl groups. This reaction is preferably carried out in the presence of an inert solvent, such as tetrahydrofuran, dioxan, chloroform, carbon disulphide, benzene, toluene or a xylene, at a temperature of from about 20 to about 140°C. and is finished after about 1 to 12 and preferably after about 2 to 6 hours.

Furthermore, compounds of general formula (I) in which R^2 signifies CSR^9, can be obtained by treating a compound of general formula (IV), wherein R^{13} is a hydrogen atom, with a thioacylating agent. As thioacylating agent, there can be used, for example, compounds of the general formula R^9—CS—E^1, wherein E^1 is a hydroxyl group or an O - alkyl, S - alkyl, S—CH_2COOH, NH_2, NH - alkyl or N(alkyl)$_2$ radical, in which the alkyl group preferably contains up to 4 carbon atoms. Of these thioacylating agents, those of general formulae R^9—CS . S . CH_2COOH and R^9—CS—NH_2 are preferred. The reaction can take place either without the use of a solvent, for example by heating the reaction components, or in the presence of one or more inert solvents; as inert solvents, there can be used, for example, water, alcohols, such as methanol or ethanol, chlorinated hydrocarbons, such as chloroform, or hydrocarbons, such as benzene or toluene. The addition of a base, such as sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, triethylamine or pyridine, is, as a rule, advantageous. The thioacylation is normally carried out at a temperature of from about 0 to about 150°C., the higher temperature range being preferred for the reaction with thioamides, for example, those of the general formula R^9—CS—NH_2. It can also be advantageous to operate under reduced pressure. As a rule, the reaction is finished after about 1 to 24 hours and preferably after about 6 to 12 hours.

Furthermore, compounds of general formula (I), wherein R^2 is a —CO—R^{11} radical, can be obtained by reacting a compound of general formula (IV) (R^{13}=H) with a compound of general formula R^{11}—CO—E. Of these compounds, chloroformic acid esters of the general formula R^{11}—CO—Cl are preferred. As a rule, the reaction takes place in the presence of an inert solvent, for example, of a chlorinated hydrocarbon, such as dichloromethane, a basic catalyst, for example pyridine or triethylamine, preferably being present. The reaction temperature is from about 0 to about 100°C. and preferably of from 20 to 60°C.

Some of the starting compounds of general formulae (II), (III) and (IV) are known; insofar as they are not known, they can be prepared according to known methods.

For example, isoquinoline derivatives of general formula (II*a*) can be obtained in that appropriately substituted 1 - cyano - 1,2 - dihydro- or 1 - cyano - 1,2,3,4 - tetrahydro - 2 - R^2 - isoquinolines are hydrogenated in the presence of Raney nickel at an elevated temperature and pressure, with migration of the R^2 substituent, to give the corresponding 1 - R^2 - aminomethyl - 1,2,3,4 - tetrahydroisoquinolines, which can subsequently be converted with acid chlorides of the general formula E—CHR^3—CX—Cl into compounds of general formula (II*a*); if, for example, chloroacetyl chloride is used in the last-mentioned stage, then compounds are obtained of general formula (II*a*) (X=O, R^3=H; E=Cl).

Compounds of general formula (II*b*) can be obtained, for example, by the reaction of appropriate 1 - aminomethyl - 1,2,3,4 - tetrahydroisoquinolines with glyoxalic acid and hydrogenation of the Schiff's bases obtained to give the corresponding 1 - carboxymethylaminomethyl - 1,2,3,4 - tetrahydroisoquinolines (II*b*) (R^1=R^2=R^3=H; X=O, E=OH); by conversion of the carboxyl group, from these there can be obtained other compounds of general formula (II*b*) in which the substituent E has a different meaning. Compounds of

general formula (II*b*) in which R^2 is a hydrogen atom, can also be obtained, for example, by hydrolysis of appropriate 2 - acyl compounds, for example, of 2 - benzoyl - 4 - oxo - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinolines; in the course of this hydrolysis, the acetyl and benzoyl radical in the 2-position can be simultaneously split off and the lactam ring opened. Furthermore, compounds of general formula (II*b*) can be obtained by various variants of the Pictet-Spengler synthesis. Thus, for example, appropriately substituted 2 - phenylethylamines can be reacted with derivatives of 2 - aminoacetaldehyde, for example, with compounds of the general formula

$$E—CX—CHR^3—NR^2—CHR^1—CH(O\text{-alkyl})_2$$

the alkyl radicals thereby preferably containing up to 4 carbon atoms.

The starting materials of general formula (II*c*) can be prepared, for example, by condensing appropriately substituted phenyl - glyoxals with aminomalonic acid diamide, 2 - aminocarbonyl - 3 - hydroxy - 5 - phenylpyrazines thereby being obtained. These can be converted by hydrolysis and decarboxylation into 3 - hydroxy - 5 - phenyl - pyrazines from which, by hydrogenation, there are obtained 3 - oxo - 5 - phenylpiperazines. Successively following reaction thereof with compounds of the general formula R^2—Cl and compounds of the general formula

$$E—CHR^4—CR^5—E$$

(whereby the two radicals E are preferably different, for example, chloroacetic acid and its derivatives) or equivalents thereof (for example, alkylene oxides) leads to the desired compounds of general formula (II*c*).

Starting materials of general formula (III) which contain a double bond in the 11*b*(1)-position, can be obtained, for example, by the Bischler-Napieralski synthesis from appropriately substituted 1 - (2 - phenylethyl) - 4 - R^2 - 2,6 - piperazinediones. Compounds of general formula (III) with a double bond in the 6(7)-position can be obtained, for example from the appropriate 7-oxo compounds by reduction and subsequent dehydration. The compounds of general formula (III) in which R^{12} is an alkylidene group can be obtained from the same 7-oxo compounds and triphenyl phosphine alkylenes.

Starting materials of general formula (III) which contain a double bond in the 11*b*(1)-position can be obtained by dehydrogenation of the corresponding saturated compounds with sulphur, selenium, chloranil or some other dehydrogenation agent. The preparation of these starting materials is especially of interest when the compounds saturated in the 11*b*(1)-position (which come within the scope of general formula (I)), are present as optically-active antipodes and are less effective than one of the other possible antipodes. In this case, the less active antipode can be converted by dehydrogenation into the compound (III) and, by subsequent hydrogenation, converted into the more active saturated racemate of general formula (I) or, by asymmetric hydrogenation, substantially converted into the more active antipodes of general formula (I).

The starting materials of general formula (IV), in which R^{13} is a hydrogen atom or a benzoyl radical, are known. The other compounds of general formula (IV) can be obtained, for example, by acylation of the compounds which are unsubstituted in the 2-position.

In a compound obtained of general formula (I), one or more of the substituents R^1 to R^8 and X can be converted into one or more other substituents R^1 to R^8 and X.

Thus, in particular, it is possible, in a compound obtained of general formula (I), by treatment with a hydroxylating agent to introduce a hydroxyl group, with a hydroxyalkylating agent to introduce a hydroxyalkyl radical, with a halogenating agent to introduce one or more halogen atoms and/or with a nitrating agent to introduce one or more nitro groups and/or by treatment with an agent giving off sulphur, to convert one or more oxo groups into thioxo groups and/or to convert a compound of general formula (I), in which R^2 is a hydrogen atom, with a thioacylating agent into the corresponding thioamide (I) (R^2=CS—R^9) or, by reaction with a compound of the formula R^{11}—CO—E, into the corresponding carbonic acid derivative (I) (R^2=CO—R^{11}). The above-described methods are thereby employed but, instead of using a compound of general formula (IV), there is used, as starting material, an appropriately substituted product of general formula (I).

Furthermore, in a compound obtained of general formula (I), groups which can be split off by solvolysis, especially acyl radicals, can be split off by treatment with a solvolysing agent and/or amino and/or hydroxyl groups can be acylated by treatment with an acylating agent and/or alkylated by treatment with an alkylating agent and/or reducible groups present, especially keto, hydroxyl and/or nitro groups and/or halogen atoms, can be reduced by treatment with a reducing agent or can be replaced by hydrogen and/or carbon-carbon double bonds present can be hydrogenated and/or amino groups present can be diazotised by treatment with nitrous acid or with a derivative thereof and the diazonium group of the compounds obtained subsequently replaced by a halogen atom or by a hydroxyl, alkoxy, cyano or Z group and/or a hydroxyl group converted by treatment with an inorganic acid halide into a halogen atom

and/or a keto group converted by treatment with a fluorination agent into a CF_2 group or by reductive amination converted into an amino group.

Solvolytic splitting off of acyl radicals or of thioacyl radicals in the 2-position and/or of acyl radicals from the substituents R^6 or R^7 (in the case in which these are acyloxy, acylamino or benzoyloxy radicals), preferably takes place by treatment with a solvolysing agent in an acidic or alkaline medium. The conditions must thereby be so selected that the lactam group is not simultaneously split off. Therefore, mild reaction conditions are preferred. As acids, there can be used for the solvolysis, for example, mineral acids, such as phosphoric acid, sulphuric acid or hydrochloric acid, as well as acid salts, such as potassium hydrogen sulphate. As bases, there can be used, for example, alkali metal or alkaline earth metal hydroxides, such as sodium, potassium, calcium or barium hydroxide, alkali metal carbonates, such as sodium or potassium carbonate, alkali metal alcoholates, such as sodium or potassium methylate or ethylate, as well as, for example, hydrazine hydrate. As a rule, the solvolysis is carried out in an aqueous, aqueous-alcoholic or alcoholic medium, for example, in methanol or ethanol; however, it is also possible to employ an excess of the acid, for example of sulphuric or phosphoric acid, in which case water can also be present. Methanolic or ethanolic hydrochloric acid can also be used as solvolysing agent. The reaction temperatures for the solvolysis are from about −50 to +200°C. and preferably from about 20 to 150°C. The solvolysis is finished after about 0.5 to 72 hours and preferably after about 2 to 48 hours.

A solvolytic splitting of alkoxy radicals, especially of aromatically - bound alkoxy radicals, in the compounds obtained of general formula (I) can be carried out with, for example, Lewis acids, such as boron tribromide, in inert solvents, such as methylene chloride or chloroform, at temperatures of from about −40 to +50°C.

An acylation of amino and/or hydroxyl groups in a compound obtained of general formula (I) can be carried out with appropriate carboxylic acids or functional derivatives thereof. For the acylation of an amino group in the 2-position, there can be used carboxylic acids of the general formula R^9—COOH, for the acylation of hydroxyl and/or amino groups which are in the aromatic nucleus, there can, on the other hand, be used fatty acids containing up to 4 carbon atoms and benzoic acid can also be used for O - acylation. As functional derivatives, there are preferably used the carboxylic acid anhydrides, for example acetic anhydride, as well as mixed carboxylic acid anhydrides, for example *p* - fluorobenzoic acid-formic acid anhydride, carboxylic acid halides, preferably the chlorides and bromides, such as acetyl chloride or bromide, and also the corresponding azides or esters, especially the alkyl esters in which the alkyl radical preferably contains up to 4 carbon atoms. When carrying out the acylation, an inorganic or organic base is advantageously added, for example, an alkali metal hydroxide or carbonate, such as sodium or potassium hydroxide or sodium or potassium carbonate, or a tertiary amine, such as triethylamine, triisopropylamine or pyridine. As a rule, the reaction is carried out in the presence of an inert solvent, for example of an ether, such as diisopropyl ether, tetrahydrofuran or dioxan, of a halogenated hydrocarbon, such as dichloromethane, chloroform, carbon tetrachloride or chlorobenzene, or of a hydrocarbon, such as benzene or toluene. However, as solvent there can also be used an excess of the carboxylic acid derivative and/or an excess of the added base. Furthermore, it is possible to produce the actual acylating agent *in situ*. For example, the carboxylic acid halides can be produced *in situ* from the carboxylic acids with the use of halogenating agents, for example, tin tetrachloride, phosphorus trichloride, phosphorus tribromide, phosphorus oxychloride, thionyl chloride or phosphorus pentachloride, the reaction thereby being carried out in the presence or absence of the above-mentioned bases and/or solvents. In carrying out the acylation, an agent splitting off water can also be added. For example, acylation can be carried out with the free carboxylic acid in the presence of a carbodiimide, such as dicyclohexyl carbodiimide, in one of the above-mentioned solvents. The reaction temperatures for the acylation can be between about 0 and about 200°C. and preferably between about 20 and 80°C. The reaction is finished after about 10 minutes to 72 hours and preferably after about 1 to 24 hours.

Acylation can also be carried out with ketenes, preferably in one of the above-mentioned solvents, with the addition of an acidic catalyst, such as *p* - toluene - sulphonic acid or sulphuric acid.

Compounds of general formula (I) which contain one or more free hydroxyl, amino or monoalkylamino radicals as substituents can be alkylated to give the corresponding alkoxy, monoalkylamino or dialkylamino compounds or to give the corresponding trialkyl ammonium salts.

The alkylation can be carried out according to conventional methods by treatment with an alkylating agent. For the O - alkylation, the starting materials are preferably first converted into corresponding salts (phenolates) by the addition of a base, for example of sodium hydroxide, potassium hydroxide or potassium carbonate. As alkylation agents, there can be used, for example, alkyl halides, such as

methyl chloride, bromide or iodide, ethyl chloride, bromide or iodide or the corresponding dialkyl sulphuric acid or alkyl sulphonic acid esters, for example dimethyl sulphate, diethyl sulphate or methyl *p* - toluene - sulphonate. Diazo compounds, such as diazomethane, can also be used for the O - alkylation. Amino compounds can be alkylated with these reagents but also reductively with aldehydes, such as formaldehyde or acetaldehyde, for example in the presence of hydrogen or formic acid. If the reaction is carried out in the presence of hydrogen, then it is expedient to add one of the catalysts which were mentioned hereinbefore for the reduction of compounds of general formula (III). As solvent, there can be used, for example, water or aqueous sodium hydroxide solution, an alcohol, such as methanol, ethanol or *n* - butanol, an ether, such as tetrahydrofuran or dioxan, an amide, such as dimethylformamide, or a hydrocarbon, such as benzene or a xylene. Solvent mixtures can also be employed. The addition of a base, for example of an alkali metal hydroxide, such as sodium or potassium hydroxide, or of a tertiary amine, such as pyridine or triethylamine, can also be useful.

In the case of the N - alkylation, depending upon the choice of the reaction conditions and of the amount of the added alkylation agent, there can be preponderantly obtained mono- or dialkylamino compounds or trialkyl ammonium salts. The reaction temperature for the alkylation is preferably of from about −10 to about 150°C. and more preferably of from about 20 to 100°C.

Furthermore, reducible groups and/or carbon-carbon double bonds present in the compounds obtained of general formula (I) can be reduced by treatment with a reducing agent or can be replaced by hydrogen. Reducible groups are, in particular, keto and/or hydroxyl groups in the 7-position, nitro groups in the 8-, 9-, 10- or 11-position or as a component of the radical R^9, for example as a substituent on a cycloalkyl, cycloalkenyl or phenyl radical, halogen atoms in the 7-, 8-, 9-, 10- or 11-position or as a component of the radical R^9, for example as a substituent on a cycloalkyl, cycloalkenyl or phenyl radical. Reducible carbon-carbon double bonds can occur especially in the radical R^9 if this is, for example, a cycloalkenyl radical.

These groups and especially carbon-carbon double bonds can be reduced according to the above-described methods of catalytic hydrogenation.

Besides the catalytic hydrogenation, other methods of reduction can also be employed. However, care must thereby be taken that the lactam or thiolactam group of the ring system is not attacked. This is, however, according to the statements in the literature, easily possible. Thus, for the reduction of, for example, keto or nitro groups, reaction with nascent hydrogen can be used, which can be produced, for example, by the treatment of metals with acids or bases. Thus, for example, there can be used the systems zinc/acid, iron/acid, tin/acid or zinc/aqueous alkali metal hydroxide solution. As acids, there can be used, for example, hydrochloric acid or acetic acid. Furthermore, as reducing agents, there can be employed: alkali metals, for example sodium, in an alcohol, such as ethanol, isopropanol or isoamyl alcohol; complex metal hydrides, which do not attack the lactam group, such as sodium borohydride, lithium borohydride or potassium trimethoxyborohydride; stannous chloride; or hydrazine. The reduction can be carried out in the presence of an additional inert solvent, those solvents being employed which are known from the literature for the individual reduction methods. Thus, for example, complex metal hydrides are used in an ether, such as diethyl ether, tetrahydrofuran, dioxan, 1,2 - dimethoxyethane or diglyme, and sodium borohydride also in alcoholic solution, for example in methanolic or ethanolic solution, or in aqueous alcoholic or aqueous solution. In general, the reduction reaction is carried out at a temperature of from about −80 to +250°C. and preferably of from −20 to +100°C.

Keto groups and especially keto groups in the 7-position can be converted into methylene groups by catalytic hydrogenation on palladium catalysts or by reaction with hydrazine and subsequent thermal decomposition of the hydrazone formed, by the Wolff-Kishner method. The last-mentioned reaction is preferably carried out in the presence of a strong base and of a high boiling solvent, such as diethylene glycol.

In a compound obtained of general formula (I) which contains one or more aromatically bound amino groups, these can be converted by diazotisation into the corresponding diazonium compounds. Diazotisation can be carried out, for example, in acidic aqueous solution, for example in the presence of sulphuric acid, hydrochloric acid, hydrobromic acid or tetrafluoroboric acid, by the addition of an inorganic nitrite, preferably of sodium or potassium nitrite, at a temperature of from about −20 to +10°C. It is also possible to use an organic nitrite, for example, *n* - butyl nitrite, *n* - amyl nitrite or isoamyl nitrite, at a temperature of from about −20 to +10°C. in an inert solvent, such as diethyl ether, tetrahydrofuran or dioxan.

The diazonium group in the diazonium compounds thus obtained can be exchanged, for example, for fluorine, chlorine, bromine, iodine, hydroxyl, alkoxy, cyano or Z groups.

For the introduction of a fluorine atom, diazotisation is carried out, for example, with anhydrous hydrofluoric acid and then subsequently heated or the diazonium salt is

reacted with tetrafluoroboric acid to give the sparingly-soluble diazonium tetrafluoroborates. These can be isolated and thermally converted into the desired fluoro compounds, for example by heating in an inert solvent. The diazonium tetrafluoroborates can also, without isolation, be decomposed in aqueous suspension by irradiation with a mercury lamp. The diazonium group can be exchanged for chlorine or bromine, preferably in hot solution, in the presence of cuprous chloride or cuprous bromide, by Sandmeyer's method. The exchange of a diazonium iodide group for iodine even takes place by slight heating, whereby there can also be added catalysts, such as cuprous iodide, bromide or chloride. Hydrolysis of the diazonium salts, preferably with heating, leads to the corresponding hydroxy compounds. The diazonium salt grouping can also be exchanged for an alkoxy radical, for example by heating in an aqueous-alcoholic solution. The replacement of the diazonium group for a cyano group can be carried out, for example, by Sandmeyer's method in the presence of cuprous cyanide and an alkali metal cyanide, such as sodium or potassium cyanide, even in the cold, for example at a temperature of from about 0 to +50°C.

The diazonium compounds can also be coupled with appropriate coupling components to give azo dyestuffs of the general formula (I), in which R^6 or R^7 are Z and/or R^9 is a Z-substituted phenyl radical. These compounds have, in comparison with the fundamental amino compounds, the advantage of being more stable and of being easier to incorporate into pharmaceutical formulations. As coupling components, there are most preferably used benzene or naphthalene derivatives which can easily be coupled, for example, those which carry in the *p*-position activating substituents, such as amino, alkylamino, dialkylamino, hydroxy or alkoxy groups, and, in addition, can also contain further substituents, such as carboxy, halogen, preferably fluorine or chlorine, sulpho or alkyl groups.

Furthermore, it is possible to convert a hydroxyl group present in the product obtained of general formula (I), especially an aliphatically-bound hydroxyl group, by treatment with an inorganic acid halide, such as thionyl chloride, phosphorus trichloride, phosphorus tribromide, or phosphorus pentachloride, into a halogen atom. It is preferable to work in the presence of an inert solvent, such as dichloromethane, chloroform or carbon tetrachloride, at a temperature of from about 20 to about 80°C.

Furthermore, it is possible to convert a keto group in the substituent R^9 into a CF_2 group, for example with sulphur tetrafluoride or phenyl sulphur trifluoride, in the presence of hydrogen fluoride or also with carbonyl difluoride in the presence of pyridine. In the case of these reactions, it is preferable to employ inert solvents, such as methylene chloride, chloroform or tetrahydrofuran. The reaction temperature can be from about 0 to 150°C. and is preferably from about 20 to 50°C. It can also be advantageous to operate under pressure.

Furthermore, a keto group in the substituent R^9 can be converted by reductive amination in one or more stages into an amino group. Thus, for example, it is possible to convert a keto group with hydroxylamine into an oxime or with hydrazine into a hydrazone and catalytically to hydrogenate the derivatives thus obtained, for example on Raney nickel, at 1 to 50 and preferably at about 5 to 10 ats. pressure. It is also possible to hydrogenate the ketone in the presence of ammonia or of a monoalkylamine or dialkylamine, preferably at a pressure of from about 1 to 200 and especially of from 80 to 120 ats. pressure. As solvents for the last-mentioned form of amination, there can be used, for example, alcohols, such as methanol, ethanol or isopropanol, as well as ethers, such as tetrahydrofuran or dioxan. Liquid ammonia can also be employed. The reaction temperatures can be from about −40 to +150°C. and preferably of from about 60 to 80°C. The reaction times needed are about 4 to 24 hours and preferably about 8 to 12 hours.

A base of general formula (I) can be converted in conventional manner with an acid into the corresponding acid-addition salt. For this reaction, those acids can be used which give physiologically compatible salts. Thus, inorganic acids can be used, for example, sulphuric acid, nitric acid, hydrohalic acids, such as hydrochloric acid, hydrobromic acid or hydriodic acid, phosphoric acids, such as orthophosphoric acid, or sulphamic acid; furthermore, organic acids, especially aliphatic, alicyclic, araliphatic, aromatic or heterocyclic mono- or polybasic carboxylic or sulphonic acids, such as formic acid, acetic acid, propionic acid, butyric acid, pivalic acid, diethylacetic acid, oxalic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, gluconic acid, citric acid, benzoic acid, salicylic acid, phenylpropionic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- and ethane - sulphonic acid, ethane - disulphonic acid, 2 - hydroxyethane - sulphonic acid, benzene - sulphonic acid, *p* - toluene - sulphonic acid, naphthalene - mono- or disulphonic acids, for example naphthalene - 1- or -2 - sulphonic acid or naphthalene - 1,5- or -2,6 - disulphonic acid, can be used.

Acidic compounds of general formula (I) and especially those which contain a phenolic hydroxyl group and/or a carboxyl group and/or a sulpho group, can, by treatment with a base, be converted into the corresponding physiologically compatible metallic or

ammonium salts. Preferred salts include the sodium, potassium, calcium, ammonium and substituted ammonium salts, for example, the cyclohexyl, benzyl or triethanol ammonium salts.

Compounds of general formula (I) which carry a primary, secondary or tertiary amino group, can, by treatment with a quaternising alkylation agent, such as a methyl or ethyl halide or dimethyl sulphate, and preferably with an excess of such an alkylation agent, be converted into their physiologically compatible quaternary ammonium salts.

The free bases of general formula (I) can, if desired, be liberated from their salts by treatment with strong bases, such as sodium or potassium hydroxide or sodium or potassium carbonate. Analogously, the acidic compounds of general formula (I) can be liberated from their metallic or ammonium salts by treatment with a strong acid, such as hydrochloric acid or sulphuric acid.

In the case of some of the above-described reactions, products are obtained of indefinite constitution. In particular, for example by halogenation or nitration of compounds of general formula (IV) or of compounds of general formula (I), wherein R^6 and R^7 are hydrogen atoms, products are formed in which the position of the newly introduced substituents is indefinite. The indefinite position of the substituents is, in the case of such compounds, indicated in the following with a question mark or with an alternative statement; "-8(?)-bromo" means, for example, that in the product in question, the bromine atom is presumably in the 8-position but that this is not definite. Similarly, "8-(or 11)-nitro", for example, means that in the compound in question, the nitro group is, in all probability, in the 8- or 11-position but that the exact position of the nitro group is not definite.

The compounds of general formula (I) possess at least one centre of asymmetry in the 11*b*-position. In the case of appropriate substitution, they can possess further centres of asymmetry. Therefore, in the case of their syntheses, they can be obtained as racemates or, if optically-active starting materials have been used, can also be obtained in optically-active form. If the compounds have two or more centres of asymmetry, then they are generally obtained from the syntheses in the form of mixtures of racemates from which the individual racemates can be isolated in pure form, for example by recrystallisation or by chromatography. However, it is also possible that only one of the possible racemates is preponderantly or exclusively obtained. This is especially the case when starting from a sterically uniform starting material. In this connection, those compounds of general formula (I) are to be particularly mentioned in which the substituent R^4 is other than hydrogen, i.e. alkyl or phenyl and especially methyl. These compounds are, in the following, called *cis* compounds when the hydrogen atom in the 6- and 11*b*-position is in the *cis* position, for example, 6 - *cis* - methyl. Otherwise, they are called *trans* compounds. The stereochemical assignment has taken place with great probability but not with absolute certainty.

Racemates obtained can, if desired, be mechanically or chemically separated into their optical antipodes by known methods. From the racemates there are preferably formed diastereomers by reaction with optically-active separating agents. For example, a racemate of general formula (I) which contains a basic group, for example an amino group, can be converted with an optically-active acid into the corresponding salt. As acids for this purpose, there can be used, for example, dextro- and laevo-rotary antipodes of tartaric acid, dibenzoyltartaric acid, diacetyltartaric acid, camphoric acid, camphor-sulphonic acids, mandelic acid, malic acid, lactic acid, 2 - phenylbutyric acid, dinitrodiphenic acid or quinic acid. Racemates of general formula (I) which contain an acidic group, for example a carboxylic acid or sulphonic acid group, can be reacted analogously with an optically-active base, for example, with strychnine, brucine, quinine or one of the optically-active forms of 1 - phenylethylamine. The diastereomeric mixtures obtained can subsequently be separated by crystallisation or by manual selection. The desired optically-active antipodes of the compounds of general formula (I) can subsequently be obtained by hydrolytic decomposition of the isolated diastereomeric salts.

The compounds of general formula (I) have an excellent activity against cestodes and trematodes. They can, for example, be used against the following cestodes (arranged according to host):

1. Ruminants: *Moniezia, Stilesia, Avitellina, Thysanosoma, Thysaniezia,* hydatids of *Taenia sp., Coenurus cerebralis, Echinococci hydatids*;
2. Ungulates: *Anoplocephala*;
3. Rodents: *Hymenolepis* (especially *H. nana* and *H. diminuta*);
4. Birds: *Davainea, Raillietina, Hymenolepis*;
5. Canines and felines: *Taenia* (especially *T. hydatigena, T. pisiformis, T. taeniaeformis, T. ovis, T. serialis, T. cervi, T. multiceps*), *Dipylidium* (especially *D. caninum*), *Echinococcus* (especially *E. granulosus* and *E. multilocularis*);
6. Humans: *Taenia* (especially *T. solium, T. saginata, T. serialis*), *Hymenolepis* (especially *H. nana* and *H. diminuta*), *Drepanidotaenia, Dipylidium, Diplopylidium, Coenurus* (especially *C. cerebralis, Diphyllobothrium*), (especially *D. latum*), *Echinococcus*

hydatids (especially *E. granulosis* and *E. multilocularis*).

The trematodes which are important to combat in human and veterinary medicine include those of the families *Schistosomidae*, especially of the genus *Schistosoma* (*Sch. mansoni*, *Sch. haemotobium* and *Sch. japonicum*). The genuses *Fasciola*, *Dicrocoelium*, *Clonorchis*, *Opisthorchis*, *Paragonimus*, *Paramphistomum*, *Echimostoma* and the like can possibly also be influenced.

The compounds of general formula (I) can be used, *inter alia*, in the following host and/or intermediate host organisms for combating cestodes or trematodes and/or their larvae: humans, types of monkeys, as well as the most important domestic and wild animals, for example, the various canines, such as dogs and foxes; felines, such as cats; ungulates, such as horses, donkeys and mules; cervids, such as roe, red and fallow deer, chamois; rodents; ruminants, such as cows, sheep and goats; birds, such as hens and ducks; pigs; and fish.

Habitats of the influencable parasites or of their larvae include, in particular, the gastro-intestinal tract, for example, the stomach, intestines, pancreas and bile duct. However, various other organs include, for example, liver, kidneys, lungs, heart, spleen, lymph nodes, brain, spinal cord and testes, the abdominal cavity, connective tissue, musculature, peritoneum, pleura, diaphragm, and blood vessels; thus, the compounds of general formula (I) act, with good compatibility, for example, against *Schistosoma sp.* in the blood vessels, against *Hymenolepis microstoma* in the bile duct and against *T. hydatigena* hydatids in the liver.

The compounds of general formula (I) can be used as such or in combination with pharmaceutically acceptable, inert carriers. Carriers of this type can include, for example, capsules, solid diluents or filler materials, sterile aqueous media and/or various non-toxic organic solvents.

Forms of administration which can be used include, for example, tablets and dragees (which can also contain the active material in depot form), effervescent tablets, capsules, granulates, aqueous suspensions, injectable solutions, emulsions and suspensions, elixirs, syrups or pastes. The formulations for this purpose can be prepared in known manner, for example, by the addition of the active materials to solvents and/or carrier materials, optionally with the use of emulsifying agents and/or dispersion agents. As adjuvants, there can be used, for example, water, non-toxic organic solvents (e.g. paraffins or alcohols, such as glycerol or polyethylene glycol), vegetable oils (e.g. sesame oil), solid carrier materials, such as natural or synthetic mineral powders (e.g. talc or highly dispersed silicic acid), sugars, emulsifiers (e.g. ionic or non-ionic), dispersion agents (e.g. methyl - cellulose or polyvinyl - pyrrolidone) and/or lubricants (e.g. magnesium stearate). Tablets can also contain additives, such as sweetening agents, sodium citrate, calcium carbonate and dicalcium phosphate, together with other additives, such as starch and gelatine. Aqueous suspensions and/or elixirs can, if desired, contain flavour improvers and/or colouring materials. The compounds (I) can, if desired, also be administered without or almost without adjuvants, for example in capsules.

The active materials (I) are preferably administered orally but parenteral, especially subcutaneous or intramuscular, as well as dermal administration is also possible.

For combating adult cestodes, it is advantageous to administer the active materials one or more times daily in amounts of from 0.01 to 250 mg./kg. and preferably of from about 0.5 to 100 mg./kg., orally or subcutaneously. In the case of combating the corresponding tapeworn larvae (hydatids) or for combating *Schistosoma*, larger amounts of active material may be necessary.

When administering comparatively large amounts of active material, they can also be divided over the course of the day into smaller individual dosages. Thus, instead of 1000 mg., there can be administered 5 separate dosages, each of 200 mg. In veterinary medicine, administration with the animal feed can also be used, in which case it is preferable first to prepare an appropriate pre-mix containing the active material. Here again, all conventional additive materials can also be used.

If necessary, it is possible to deviate from the above-mentioned amounts, depending upon the body weight or the nature of the route of application but also on the basis of species and of the individual behaviour thereof towards the medicament or the nature of its formulation or the point of time or interval at which administration takes place. Thus, in some cases, it can suffice to administer less than the above-mentioned minimum amount, whereas, in other cases, it is necessary to exceed the upper limit.

Depending upon the nature of the administration, the ratio between the compounds (I) and the carrier and/or adjuvant employed can vary very considerably. If, for example, a compound (I) is administered as a tablet or dragee, then about 0.01 to 2500 mg. of active material can be combined with about 1 to 10,000 mg. of adjuvant. If, on the other hand, a compound (I) is formulated as a pre-mix for a medicated feed, then for each 1 kg. of carrier or adjuvant material, there can be used about 0.1 to 400 g. of compound (I). When formulated as an injection liquid, a solution of 1 litre of liquid can contain, depending upon the nature of the solubilising agent, about 0.5 to 100 g. of a compound (I);

similarly, 1 litre of syrup can contain dissolved or suspended therein about 0.5 to 250 g. of a compound (I).

The compounds (I) can also be present in the formulations in admixture with other active materials. Thus, for the achievement of a broader spectrum of activity, it is sometimes useful to add an active material which acts against nematodes, for example, thiabendazole [2 - (4 - thiazolyl) - benzimidazole] or piperazine (or piperazine derivatives, such as N - methylpiperazine). It is also possible to administer a mixture of two or more compounds of general formula (I).

In the following Examples, which are given for the purpose of illustrating the present invention, the "usual working up" means the following procedure: if necessary, there is added water and/or an organic extraction agent, such as dichloromethane, chloroform or an ether, followed by separation, washing the organic phase with dilute hydrochloric acid (provided that the product is not basic) and with water, separation, drying over anhydrous magnesium or sodium sulphate, evaporation and purification of the crude product by crystallisation and/or chromatography. The infra-red spectra are measured in potassium bromide. The abbreviation "HPI" employed in the following Examples means "1,2,3,6,7,11b - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline":

Example 1

a) 300 ml. of a 20% *n* - butyl lithium solution in hexane are added, under an atmosphere of nitrogen, at 5—10°C. and with vigorous stirring to 216 g. N - (2 - chloroacetyl - 3 - *cis* - methyl - 1,2,3,4 - tetrahydroisoquinolyl - 1 - methyl) - benzamide (m.p. 140°C.; obtainable from N - (3 - *cis* - methyl - 1,2,3,4 - tetrahydroisoquinolyl - 1 - methyl) - benzamide by reaction with chloroacetyl chloride) in 4 litres anhydrous tetrahydrofuran. The reaction mixture is stirred for 2 hours at 20°C., then hydrolysed with water, whereafter the solvent is evaporated off and the residue worked up as usual to give 2 - benzoyl - 4 - oxo - 6 - *cis* - methyl - HPI which, after recrystallisation from methanol, melts at 165°C.

The following compounds are obtained in an analogous manner by cyclising the appropriate isoquinoline derivatives:

2 - acetyl - 4 - oxo - 6 - *cis* - methyl - HPI
2 - propionyl - 4 - oxo - 6 - *cis* - methyl - HPI
2 - butyryl - 4 - oxo - 6 - *cis* - methyl - HPI
2 - isobutyryl - 4 - oxo - 6 - *cis* - methyl - HPI; m.p. 136°C.
1 - methyl - 2 - isobutyryl - 4 - oxo - HPI
2 - isobutyryl - 3 - methyl - 4 - oxo - HPI
2 - isobutyryl - 4 - oxo - 6 - *cis* - methyl - HPI
2 - isobutyryl - 4 - oxo - 6 - *trans* - methyl - HPI
2 - isobutyryl - 4 - oxo - 7 - methyl - HPI
2 - isobutyryl - 4 - oxo - 8 - methyl - HPI
2 - isobutyryl - 4 - oxo - 9 - methyl - HPI
2 - isobutyryl - 4 - oxo - 10 - methyl - HPI
2 - isobutyryl - 4 - oxo - 11 - methyl - HPI
2 - isobutyryl - 4 - oxo - 11b - methyl - HPI
2 - valeryl - 4 - oxo - 6 - *cis* - methyl - HPI
2 - trimethylacetyl - 4 - oxo - 6 - *cis* - methyl - HPI
2 - capronyl - 4 - oxo - 6 - *cis* - methyl - HPI
2 - oenanthoyl - 4 - oxo - 6 - *cis* - methyl - HPI
1 - methyl - 2 - cyclohexylcarbonyl - 4 - oxo - HPI
1 - *n* - butyl - 2 - cyclohexylcarbonyl - 4 - oxo - HPI
2 - cyclohexylcarbonyl - 3 - methyl - 4 - oxo - HPI
2 - cyclohexylcarbonyl - 3 - ethyl - 4 - oxo - HPI
2 - cyclohexylcarbonyl - 3 - *n* - butyl - 4 - oxo - HPI
2 - cyclohexylcarbonyl - 4 - oxo - 6 - *cis* - methyl - HPI
2 - cyclohexylcarbonyl - 4 - oxo - 6 - *trans* - methyl - HPI; m.p. 134°C.
2 - cyclohexylcarbonyl - 4 - oxo - 5 - *cis* - ethyl - HPI
2 - cyclohexylcarbonyl - 4 - oxo - 6 - *trans* - ethyl - HPI
2 - cyclohexylcarbonyl - 4 - oxo - 6 - *cis* - isopropyl - HPI
2 - cyclohexylcarbonyl - 4 - oxo - 6 - *trans* - isopropyl - HPI
2 - cyclohexylcarbonyl - 4 - oxo - 6 - *cis* - phenyl - HPI
2 - cyclohexylcarbonyl - 4 - oxo - 6 - *trans* - phenyl - HPI
2 - cyclohexylcarbonyl - 4 - oxo - 7 - methyl - HPI
2 - cyclohexylcarbonyl - 4 - oxo - 7 - ethyl - HPI
2 - cyclohexylcarbonyl - 4 - oxo - 7 - phenyl - HPI
2 - cyclohexylcarbonyl - 4 - oxo - 8 - methyl - HPI
2 - cyclohexylcarbonyl - 4 - oxo - 8 - ethyl - HPI
2 - cyclohexylcarbonyl - 4 - oxo - 9 - methyl - HPI

2 - cyclohexylcarbonyl - 4 - oxo - 9 - ethyl - HPI

2 - cyclohexylcarbonyl - 4 - oxo - 10 - methyl - HPI

2 - cyclohexylcarbonyl - 4 - oxo - 10 - ethyl - HPI

2 - cyclohexylcarbonyl - 4 - oxo - 11 - methyl - HPI

2 - cyclohexylcarbonyl - 4 - oxo - 11 - ethyl - HPI

2 - cyclohexylcarbonyl - 4 - oxo - 11*b* - methyl - HPI; m.p. 143°C.

2 - cyclohexylcarbonyl - 4 - oxo - 11*b* - ethyl - HPI

2 - cyclohexylcarbonyl - 4 - oxo - 11*b* - *n* - butyl - HPI

2 - cyclohexylcarbonyl - 4 - oxo - 9,10 - dimethoxy - HPI

1 - methyl - 2 - (4 - oxo - cyclohexylcarbonyl) - 4 - oxo - HPI

2 - (4 - oxo - cyclohexylcarbonyl) - 3 - methyl - 4 - oxo - HPI

2 - (4 - oxo - cyclohexylcarbonyl) - 4 - oxo - 6 - *cis* - methyl - HPI

2 - (4 - oxo - cyclohexylcarbonyl) - 4 - oxo - 6 - *trans* - methyl - HPI; m.p. 118—120°C.

2 - (4 - oxo - cyclohexylcarbonyl) - 4 - oxo - 7 - methyl - HPI

2 - (4 - oxo - cyclohexylcarbonyl) - 4 - oxo - 8 - methyl - HPI

2 - (4 - oxo - cyclohexylcarbonyl) - 4 - oxo - 9 - methyl - HPI

2 - (4 - oxo - cyclohexylcarbonyl) - 4 - oxo - 10 - methyl - HPI

2 - (4 - oxo - cyclohexylcarbonyl) - 4 - oxo - 11 - methyl - HPI

2 - (4 - oxo - cyclohexylcarbonyl) - 4 - oxo - 11*b* - methyl - HPI

1 - methyl - 2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - HPI

2 - (tetrahydropyranyl - 4 - carbonyl) - 3 - methyl - 4 - oxo - HPI

2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - 6 - *cis* - methyl - HPI; m.p. 156—159°C.

2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - 6 - *trans* - methyl - HPI

2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - 7 - methyl - HPI

2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - 8 - methyl - HPI

2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - 9 - methyl - HPI

2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - 10 - methyl - HPI

2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - 11 - methyl - HPI

2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - 11*b* - methyl - HPI

1 - methyl - 2 - (thiacyclohexyl - 4 - carbonyl) - 4 - oxo - HPI

2 - (thiacyclohexyl - 4 - carbonyl) - 3 - methyl - 4 - oxo - HPI

2 - (thiacyclohexyl - 4 - carbonyl) - 4 - oxo - 6 - *cis* - methyl - HPI

2 - (thiacyclohexyl - 4 - carbonyl) - 4 - oxo - 6 - *trans* - methyl - HPI

2 - (thiacyclohexyl - 4 - carbonyl) - 4 - oxo - 7 - methyl - HPI

2 - (thiacyclohexyl - 4 - carbonyl) - 4 - oxo - 8 - methyl - HPI

2 - (thiacyclohexyl - 4 - carbonyl) - 4 - oxo - 9 - methyl - HPI

2 - (thiacyclohexyl - 4 - carbonyl) - 4 - oxo - 10 - methyl - HPI

2 - (thiacyclohexyl - 4 - carbonyl) - 4 - oxo - 11 - methyl - HPI

2 - (thiacyclohexyl - 4 - carbonyl) - 4 - oxo - 11*b* - methyl - HPI

1 - methyl - 2 - benzoyl - 4 - oxo - HPI

2 - benzoyl - 3 - methyl - 4 - oxo - HPI; m.p. 176°C.

2 - benzoyl - 3 - ethyl - 4 - oxo - HPI

2 - benzoyl - 3 - *n* - propyl - 4 - oxo - HPI

2 - benzoyl - 3 - isopropyl - 4 - oxo - HPI

2 - benzoyl - 3 - *n* - butyl - 4 - oxo - HPI

2 - benzoyl - 4 - oxo - 6 - *trans* - methyl - HPI; m.p. 195°C.

2 - benzoyl - 4 - oxo - 6 - *cis* - ethyl - HPI

2 - benzoyl - 4 - oxo - 6 - *trans* - ethyl - HPI

2 - benzoyl - 4 - oxo - 6 - *cis* - *n* - propyl - HPI

2 - benzoyl - 4 - oxo - 6 - *trans* - *n* - propyl - HPI

2 - benzoyl - 4 - oxo - 6 - *cis* - isopropyl - HPI

2 - benzoyl - 4 - oxo - 6 - *trans* - isopropyl - HPI

2 - benzoyl - 4 - oxo - 6 - *cis* - *n* - butyl - HPI

2 - benzoyl - 4 - oxo - 6 - *trans* - *n* - butyl - HPI

2 - benzoyl - 4 - oxo - 6 - *cis* - isobutyl - HPI

2 - benzoyl - 4 - oxo - 6 - *trans* - isobutyl - HPI

2 - benzoyl - 4 - oxo - 6 - *cis* - *sec.* - butyl - HPI

2 - benzoyl - 4 - oxo - 6 - *trans* - *sec.* - butyl - HPI

2 - benzoyl - 4 - oxo - 6 - *cis* - *tert.* - butyl - HPI

2 - benzoyl - 4 - oxo - 6 - *trans* - *tert.* - butyl - HPI

2 - benzoyl - 4 - oxo - 6 - *cis* - phenyl - HPI

2 - benzoyl - 4 - oxo - 6 - *trans* - phenyl - HPI

2 - benzoyl - 4 - oxo - 7 - methyl - HPI; m.p. 157°C.

2 - benzoyl - 4 - oxo - 7 - ethyl - HPI

2 - benzoyl - 4 - oxo - 7 - *n* - propyl - HPI

2 - benzoyl - 4 - oxo - 7 - isopropyl - HPI

2 - benzoyl - 4 - oxo - 7 - *n* - butyl - HPI

2 - benzoyl - 4 - oxo - 7 - isobutyl - HPI

2 - benzoyl - 4 - oxo - 7 - *sec.* - butyl - HPI

2 - benzoyl - 4 - oxo 7 - *tert.* - butyl - HPI

2 - benzoyl - 4 - oxo - 8 - methyl - HPI

2 - benzoyl - 4 - oxo - 8 - ethyl - HPI

2 - benzoyl - 4 - oxo 9 - methyl - HPI; m.p. 162—163°C.

2 - benzoyl - 4 - oxo - 9 - ethyl - HPI

2 - benzoyl - 4 - oxo - 10 - methyl - HPI

2 - benzoyl - 4 - oxo - 10 - ethyl - HPI

2 - benzoyl - 4 - oxo - 11 - methyl - HPI

2 - benzoyl - 4 - oxo - 11 - ethyl - HPI

2 - benzoyl - 4 - oxo - 11*b* - methyl - HPI

2 - benzoyl - 4 - oxo - 11*b* - ethyl - HPI

2 - benzoyl - 4 - oxo - 9,10 - dimethoxy - HPI; m.p. 130°C.

2 - benzoyl - 4 - oxo - 9,10 - diethoxy - HPI

2 - benzoyl - 4 - oxo - 9,10 - diacetoxy - HPI

2 - benzoyl - 4 - oxo - 9,10 - dibenzoyloxy - HPI

1 - methyl - 2 - (3 - fluorobenzoyl) - 4 - oxo - HPI

2 - (3 - fluorobenzoyl) - 3 - methyl - 4 - oxo - HPI

2 - (3 - fluorobenzoyl) - 4 - oxo - 6 - *cis* - methyl - HPI

2 - (3 - fluorobenzoyl) - 4 - oxo - 6 - *trans* - methyl - HPI

2 - (3 - fluorobenzoyl) - 4 - oxo - 7 - methyl - HPI

2 - (3 - fluorobenzoyl) - 4 - oxo - 8 - methyl - HPI

2 - (3 - fluorobenzoyl) - 4 - oxo - 9 - methyl - HPI

2 - (3 - fluorobenzoyl) - 4 - oxo - 10 - methyl - HPI

2 - (3 - fluorobenzoyl) - 4 - oxo - 11 - methyl - HPI

2 - (3 - fluorobenzoyl) - 4 - oxo - 11*b* - methyl - HPI

1 - methyl - 2 - (4 - fluorobenzoyl) - 4 - oxo - HPI

2 - (4 - fluorobenzoyl) - 3 - methyl - 4 - oxo - HPI

2 - (4 - fluorobenzoyl) - 4 - oxo - 6 - *cis* - methyl - HPI

2 - (4 - fluorobenzoyl) - 4 - oxo - 6 - *trans* - methyl - HPI; m.p. 158°C.

2 - (4 - fluorobenzoyl) - 4 - oxo - 7 - methyl - HPI

2 - (4 - fluorobenzoyl) - 4 - oxo - 8 - methyl - HPI

2 - (4 - fluorobenzoyl) - 4 - oxo - 9 - methyl - HPI

2 - (4 - fluorobenzoyl) - 4 - oxo - 10 - methyl - HPI

2 - (4 - fluorobenzoyl) - 4 - oxo - 11 - methyl - HPI

2 - (4 - fluorobenzoyl) - 4 - oxo - 11*b* - methyl - HPI

b) 15 g. boron tribromide are added dropwise at 5—10°C. to 6 g. 2 - benzoyl - 4 - oxo - 9,10 - dimethoxy - HPI in 100 ml. dichloromethane, whereafter the reaction mixture is stirred for an hour at 20°C. and then poured on to ice. The crystals which separate out are washed with water, dissolved in 200 ml. hot methanol and mixed with 50 ml. 12.5% hydrochloric acid. After an hour, the reaction mixture is evaporated and worked up as usual. There is obtained 2 - benzoyl - 4 - oxo - 9,10 - dihydroxy - HPI which, after recrystallisation from methanol, melts at 140°C.

c) 5.5 g. 2 - benzoyl - 4 - oxo - 9,10 - dibenzoyloxy - HPI are stirred in 200 ml. 10% aqueous sodium hydroxide solution for 12 hours at 20°C., insoluble material is then filtered off and the filtrate is then acidified with hydrochloric acid and worked up as usual to give 2 - benzoyl - 4 - oxo - 9,10 - dihydroxy - HPI, which melts at 140°C.

d) 3.4 g. 2 - benzoyl - 4 - oxo - 9,10 - dihydroxy - HPI in 100 ml. methanol are mixed with an excess of ethereal diazomethane solution until a pale yellow coloration remains, whereafter the reaction mixture is evaporated to give 2 - benzoyl - 4 - oxo - 9,10 - dimethoxy - HPI which, after recrystallisation from ethanol/ether, melts at 130°C.

e) 1.15 g. sodium borohydride is added portionwise at 0°C. to 6.8 g. 2 - (4 - oxo - cyclohexylcarbonyl) - 4 - oxo - 6 - *cis* - methyl - HPI in 100 ml. ethanol, whereafter the reaction mixture is stirred for 12 hours at 20°C. and then poured on to ice. There is thus obtained 2 - (4 - hydroxycyclohexylcarbonyl) - 4 - oxo - 6 - *cis* - methyl - HPI in the form of an amorphous isomeric mixture.

f) 6.8 g. 2 - (4 - oxo - cyclohexylcarbonyl) - 4 - oxo - 6 - *trans* - methyl - HPI in 100 ml. methanol are hydrogenated in the presence

of 2 g. Raney nickel for 2 hours at 50°C. and 100 ats. pressure and then filtered and the filtrate is evaporated to give 2 - (4 - hydroxycyclohexylcarbonyl) - 4 - oxo - 6 - *trans* - methyl - HPI in the form of an amorphous isomeric mixture.

g) 3.4 g. 2 - (4 - oxo - cyclohexylcarbonyl) - 4 - oxo - 6 - trans - methyl - HPI, 0.2 ml. water, 3.2 g. sulphur tetrafluoride and 50 ml. dichloromethane are shaken in an autoclave for 24 hours at 30°C., whereafter the reaction mixture is poured into a dilute aqueous solution of sodium carbonate and worked up as usual to give 2 - (4,4 - difluorocyclohexylcarbonyl) - 4 - oxo - 6 - *trans* - methyl - HPI.

h) 135 g. 2 - benzoyl - 4 - oxo - 6 - *cis* - methyl - HPI are boiled in 1.5 litres 25% hydrochloric acid and 100 ml. methanol for 12 hours, whereafter the reaction mixture is cooled, the benzoic acid which separates out is filtered off and the filtrate is washed with diethyl ether. The crude product obtained after working up in the usual way is heated for 2 hours at 16 mm.Hg. at 200°C. and the reaction mixture, after cooling, is dissolved in water and washed with ether. The aqueous phase is rendered alkaline, extracted with chloroform and worked up as usual. There is obtained 4 - oxo - 6 - *cis* - methyl - HPI which, after recrystallisation from benzene/petroleum ether, melts at 119—120°C.

Example 2

a) 1 - Carboxymethylaminomethyl - 3 - *cis* - methyl - 1,2,3,4 - tetrahydroisoquinoline hydrochloride (obtained by the reaction of 1 - aminomethyl - 3 - *cis* - methyl - 1,2,3,4 - tetrahydroisoquinoline monohydrochloride with chloroacetic acid in dimethylformamide) is heated for 2 hours at 12 mm.Hg. at 195°C., then cooled, dissolved in water, washed with ether and rendered alkaline. After extraction with chloroform and the usual working up, there is obtained 4 - oxo - 6 - *cis* - methyl - HPI, which melts at 119—120°C.

The following compounds are obtained analogously by ring closure of the appropriate tetrahydroisoquinolines:

1 - methyl - 4 - oxo - HPI
1 - ethyl - 4 - oxo - HPI
3 - methyl - 4 - oxo - HPI
3 - ethyl - 4 - oxo - HPI
3 - *n* - propyl - 4 - oxo - HPI
3 - isopropyl - 4 - oxo - HPI
3 - *n* - butyl - 4 - oxo - HPI
3 - isobutyl - 4 - oxo - HPI
3 - *tert* - butyl - 4 - oxo - HPI
4 - oxo - 6 - *trans* - methyl - HPI; m.p. 135—136°C.
4 - oxo - 6 - *cis* - ethyl - HPI
4 - oxo - 6 - *trans* - ethyl - HPI
4 - oxo - 6 - *cis* - *n* - propyl - HPI
4 - oxo - 6 - *trans* - *n* - propyl - HPI
4 - oxo - 6 - *cis* - isopropyl - HPI
4 - oxo - 6 - *trans* - isopropyl - HPI
4 - oxo - 6 - *cis* - *n* - butyl - HPI
4 - oxo - 6 - *trans* - *n* - butyl - HPI
4 - oxo - 6 - *cis* - isobutyl - HPI
4 - oxo - 6 - *trans* - isobutyl - HPI
4 - oxo - 6 - *cis* - *sec.* - butyl - HPI
4 - oxo - 6 - *trans* - *sec.* - butyl - HPI
4 - oxo - 6 - *cis* - *tert.* - butyl - HPI
4 - oxo - 6 - *trans* - *tert.* - butyl - HPI
4 - oxo - 7 - methyl - HPI
4 - oxo - 7 - ethyl - HPI
4 - oxo - 8 - methyl - HPI
4 - oxo - 8 - *n* - butyl - HPI
4 - oxo - 8 - hydroxy - HPI
4 - oxo - 8 - methoxy - HPI
4 - oxo - 8 - amino - HPI
4 - oxo - 8 - methylamino - HPI
4 - oxo - 8 - dimethylamino - HPI
4 - oxo - 8 - nitro - HPI
4 - oxo - 8 - fluoro - HPI
4 - oxo - 8 - chloro - HPI
4 - oxo - 9 - methyl - HPI
4 - oxo - 9 - hydroxy - HPI
4 - oxo - 9 - methoxy - HPI
4 - oxo - 9 - amino - HPI
4 - oxo - 9 - methylamino - HPI
4 - oxo - 9 - dimethylamino - HPI
4 - oxo - 9 - nitro - HPI
4 - oxo - 9 - fluoro - HPI
4 - oxo - 9 - chloro - HPI
4 - oxo - 10 - methyl - HPI
4 - oxo - 10 - hydroxy - HPI
4 - oxo - 10 - methoxy - HPI
4 - oxo - 10 - amino - HPI
4 - oxo - 10 - methylamino - HPI
4 - oxo - 10 - dimethylamino - HPI
4 - oxo - 10 - nitro - HPI
4 - oxo - 10 - fluoro - HPI
4 - oxo - 10 - chloro - HPI
4 - oxo - 11 - methyl - HPI
4 - oxo - 11 - hydroxy - HPI
4 - oxo - 11 - methoxy - HPI
4 - oxo - 11 - amino - HPI
4 - oxo - 11 - methylamino - HPI
4 - oxo - 11 - dimethylamino - HPI
4 - oxo - 11 - nitro - HPI
4 - oxo - 11 - fluoro - HPI
4 - oxo - 11 - chloro - HPI
4 - oxo - 11*b* - methyl - HPI
4 - oxo - 11*b* - ethyl - HPI

b) 5.5 g. 4 - nitrobenzoyl chloride in 100 ml. chloroform are added to 5 g. 4 - oxo - 6 - *cis* - methyl - HPI and 6 ml. triethylamine in 100 ml. chloroform, whereby the temperature increases to 50°C. After an hour, the reaction mixture is washed with water and then worked up as usual to give 2 - (4 - nitrobenzoyl) - 4 - oxo - 6 - *cis* - methyl - HPI which, after recrystallisation from ethanol, melts at 225—226°C.

The following compounds are obtained

analogously by acylating the appropriate compounds which are unsubstituted in the 2-position:

1 - methyl - 2 - (3 - nitrobenzoyl) - 4 - oxo - HPI

2 - (3 - nitrobenzoyl) - 3 - methyl - 4 - oxo - HPI

2 - (3 - nitrobenzoyl) - 4 - oxo - 6 - *cis* - methyl - HPI; m.p. 184—185°C.

2 - (3 - nitrobenzoyl) - 4 - oxo - 6 - *trans* - methyl - HPI; m.p. 90—92°C.

2 - (3 - nitrobenzoyl) - 4 - oxo - 7 - methyl - HPI

2 - (3 - nitrobenzoyl) - 4 - oxo - 8 - methyl - HPI

2 - (3 - nitrobenzoyl) - 4 - oxo - 8 - nitro - HPI

2 - (3 - nitrobenzoyl) - 4 - oxo - 8 - fluoro - HPI

2 - (3 - nitrobenzoyl) - 4 - oxo - 8 - chloro - HPI

2 - (3 - nitrobenzoyl) - 4 - oxo - 9 - methyl - HPI

2 - (3 - nitrobenzoyl) - 4 - oxo - 9 - nitro - HPI

2 - (3 - nitrobenzoyl) - 4 - oxo - 9 - fluoro - HPI

2 - (3 - nitrobenzoyl) - 4 - oxo - 9 - chloro - HPI

2 - (3 - nitrobenzoyl) - 4 - oxo - 10 - methyl - HPI

2 - (3 - nitrobenzoyl) - 4 - oxo - 10 - nitro - HPI

2 - (3 - nitrobenzoyl) - 4 - oxo - 10 - fluoro - HPI

2 - (3 - nitrobenzoyl) - 4 - oxo - 10 - chloro - HPI

2 - (3 - nitrobenzoyl) - 4 - oxo - 11 - methyl - HPI

2 - (3 - nitrobenzoyl) - 4 - oxo - 11 - nitro - HPI

2 - (3 - nitrobenzoyl) - 4 - oxo - 11 - fluoro - HPI

2 - (3 - nitrobenzoyl) - 4 - oxo - 11 - chloro - HPI

2 - (3 - nitrobenzoyl) - 4 - oxo - 11*b* - methyl - HPI

1 - methyl - 2 - (4 - nitrobenzoyl) - 4 - oxo - HPI

2 - (4 - nitrobenzoyl) - 3 - methyl - 4 - oxo - HPI

2 - (4 - nitrobenzoyl) - 4 - oxo - 6 - *trans* - methyl - HPI

2 - (4 - nitrobenzoyl) - 4 - oxo - 7 - methyl - HPI

2 - (4 - nitrobenzoyl) - 4 - oxo - 8 - methyl - HPI

2 - (4 - nitrobenzoyl) - 4 - oxo - 8 - nitro - HPI

2 - (4 - nitrobenzoyl) - 4 - oxo - 8 - fluoro - HPI

2 - (4 - nitrobenzoyl) - 4 - oxo - 8 - chloro - HPI

2 - (4 - nitrobenzoyl) - 4 - oxo - 9 - methyl - HPI

2 - (4 - nitrobenzoyl) - 4 - oxo - 9 - nitro - HPI

2 - (4 - nitrobenzoyl) - 4 - oxo - 9 - fluoro - HPI

2 - (4 - nitrobenzoyl) - 4 - oxo - 9 - chloro - HPI

2 - (4 - nitrobenzoyl) - 4 - oxo - 10 - methyl - HPI

2 - (4 - nitrobenzoyl) - 4 - oxo - 10 - nitro - HPI

2 - (4 - nitrobenzoyl) - 4 - oxo - 10 - fluoro - HPI

2 - (4 - nitrobenzoyl) - 4 - oxo - 10 - chloro - HPI

2 - (4 - nitrobenzoyl) - 4 - oxo - 11 - methyl - HPI

2 - (4 - nitrobenzoyl) - 4 - oxo - 11 - nitro - HPI

2 - (4 - nitrobenzoyl) - 4 - oxo - 11 - fluoro - HPI

2 - (4 - nitrobenzoyl) - 4 - oxo - 11 - chloro - HPI

2 - (4 - nitrobenzoyl) - 4 - oxo - 11*b* - methyl - HPI

1 - methyl - 2 - (2 - fluorobenzoyl) - 4 - oxo - HPI

2 - (2 - fluorobenzoyl) - 3 - methyl - 4 - oxo - HPI

2 - (2 - fluorobenzoyl) - 4 - oxo - 6 - *cis* - methyl - HPI

2 - (2 - fluorobenzoyl) - 4 - oxo - 6 - *trans* - methyl - HPI

2 - (2 - fluorobenzoyl) - 4 - oxo - 7 - methyl - HPI

2 - (2 - fluorobenzoyl) - 4 - oxo - 8 - methyl - HPI

2 - (2 - fluorobenzoyl) - 4 - oxo - 8 - nitro - HPI

2 - (2 - fluorobenzoyl) - 4 - oxo - 8 - fluoro - HPI

2 - (2 - fluorobenzoyl) - 4 - oxo - 8 - chloro - HPI

2 - (2 - fluorobenzoyl) - 4 - oxo - 9 - methyl - HPI

2 - (2 - fluorobenzoyl) - 4 - oxo - 9 - nitro - HPI

2 - (2 - fluorobenzoyl) - 4 - oxo - 9 - fluoro - HPI

2 - (2 - fluorobenzoyl) - 4 - oxo - 9 - chloro - HPI

2 - (2 - fluorobenzoyl) - 4 - oxo - 10 - methyl - HPI

2 - (2 - fluorobenzoyl) - 4 - oxo - 10 - nitro - HPI

2 - (2 - fluorobenzoyl) - 4 - oxo - 10 - fluoro - HPI

2 - (2 - fluorobenzoyl) - 4 - oxo - 10 - chloro - HPI

2 - (2 - fluorobenzoyl) - 4 - oxo - 11 - methyl - HPI

2 - (2 - fluorobenzoyl) - 4 - oxo - 11 - nitro - HPI

2 - (2 - fluorobenzoyl) - 4 - oxo - 11 - fluoro - HPI

2 - (2 - fluorobenzoyl) - 4 - oxo - 11 - chloro - HPI
2 - (2 - fluorobenzoyl) - 4 - oxo - 11*b* - methyl - HPI
1 - methyl - 2 - (3 - fluorobenzoyl) - 4 - oxo - HPI
2 - (3 - fluorobenzoyl) - 3 - methyl - 4 - oxo - HPI
2 - (3 - fluorobenzoyl) - 4 - oxo - 6 - *cis* - methyl - HPI
2 - (3 - fluorobenzoyl) - 4 - oxo - 6 - *trans* - methyl - HPI
2 - (3 - fluorobenzoyl) - 4 - oxo - 7 - methyl - HPI
2 - (3 - fluorobenzoyl) - 4 - oxo - 8 - methyl - HPI
2 - (3 - fluorobenzoyl) - 4 - oxo - 8 - nitro - HPI
2 - (3 - fluorobenzoyl) - 4 - oxo - 8 - fluoro - HPI
2 - (3 - fluorobenzoyl) - 4 - oxo - 8 - chloro - HPI
2 - (3 - fluorobenzoyl) - 4 - oxo - 9 - nitro - HPI
2 - (3 - fluorobenzoyl) - 4 - oxo - 9 - fluoro - HPI
2 - (3 - fluorobenzoyl) - 4 - oxo - 9 - chloro - HPI
2 - (3 - fluorobenzoyl) - 4 - oxo - 10 - nitro - HPI
2 - (3 - fluorobenzoyl) - 4 - oxo - 10 - fluoro - HPI
2 - (3 - fluorobenzoyl) - 4 - oxo - 10 - chloro - HPI
2 - (3 - fluorobenzoyl) - 4 - oxo - 11 - nitro - HPI
2 - (3 - fluorobenzoyl) - 4 - oxo - 11 - fluoro - HPI
2 - (3 - fluorobenzoyl) - 4 - oxo - 11 - chloro - HPI
2 - (4 - fluorobenzoyl) - 4 - oxo - 8 - nitro - HPI
2 - (4 - fluorobenzoyl) - 4 - oxo - 8 - fluoro - HPI
2 - (4 - fluorobenzoyl) - 4 - oxo - 8 - chloro - HPI
2 - (4 - fluorobenzoyl) - 4 - oxo - 9 - nitro - HPI
2 - (4 - fluorobenzoyl) - 4 - oxo - 9 - fluoro - HPI
2 - (4 - fluorobenzoyl) - 4 - oxo - 9 - chloro - HPI
2 - (4 - fluorobenzoyl) - 4 - oxo - 10 - nitro - HPI
2 - (4 - fluorobenzoyl) - 4 - oxo - 10 - fluoro - HPI
2 - (4 - fluorobenzoyl) - 4 - oxo - 10 - chloro - HPI
2 - (4 - fluorobenzoyl) - 4 - oxo - 11 - nitro - HPI
2 - (4 - fluorobenzoyl) - 4 - oxo - 11 - fluoro - HPI
2 - (4 - fluorobenzoyl) - 4 - oxo - 11 - chloro - HPI
2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - 8 - nitro - HPI
2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - 8 - fluoro - HPI
2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - 8 - chloro - HPI
2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - 9 - nitro - HPI
2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - 9 - fluoro - HPI
2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - 9 - chloro - HPI
2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - 10 - nitro - HPI
2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - 10 - fluoro - HPI
2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - 10 - chloro - HPI
2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - 11 - nitro - HPI
2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - 11 - fluoro - HPI
2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - 11 - chloro - HPI
2 - (thiacyclohexyl - 4 - carbonyl) - 4 - oxo - 8 - nitro - HPI
2 - (thiacyclohexyl - 4 - carbonyl) - 4 - oxo - 8 - fluoro - HPI
2 - (thiacyclohexyl - 4 - carbonyl) - 4 - oxo - 8 - chloro - HPI
2 - (thiacyclohexyl - 4 - carbonyl) - 4 - oxo - 9 - nitro - HPI
2 - (thiacyclohexyl - 4 - carbonyl) - 4 - oxo - 9 - fluoro - HPI
2 - (thiacyclohexyl - 4 - carbonyl) - 4 - oxo - 9 - chloro - HPI
2 - (thiacyclohexyl - 4 - carbonyl) - 4 - oxo - 10 - nitro - HPI
2 - (thiacyclohexyl - 4 - carbonyl) - 4 - oxo - 10 - fluoro - HPI
2 - (thiacyclohexyl - 4 - carbonyl) - 4 - oxo - 10 - chloro - HPI
2 - (thiacyclohexyl - 4 - carbonyl) - 4 - oxo - 11 - nitro - HPI
2 - (thiacyclohexyl - 4 - carbonyl) - 4 - oxo - 11 - fluoro - HPI
2 - (thiacyclohexyl - 4 - carbonyl) - 4 - oxo - 11 - chloro - HPI

c) 2.4 g. thionyl chloride are added dropwise at −40°C. to a solution of 2.9 g. cyclohexanone - 4 - carboxylic acid in 20 ml. dimethylformamide and 50 ml. dichloromethane, whereafter the reaction mixture is stirred for 30 minutes and then 4.3 g. 4 - oxo - 6 - *trans* - methyl - HPI and 4.1 g. triethylamine in 50 ml. dichloromethane are added thereto, followed by stirring for one hour and thereafter working up as usual. There is obtained 2 - (4 - oxo - cyclohexylcarbonyl) - 4 - oxo - 6 - *trans* - methyl - HPI which, after recrystallisation from diethyl ether, melts at 118—120°C.

The following compounds are obtained in

an analogous manner by acylation of the appropriate compounds:

1 - methyl - 2 - (cyclohexene - 4 - carbonyl) - 4 - xo - HPI
2 - (cyclohexene - 4 - carbonyl) - 3 - methyl - 4 - oxo - HPI
2 - (cyclohexene - 4 - carbonyl) - 4 - oxo - 6 - *cis* - methyl - HPI
2 - (cyclohexene - 4 - carbonyl) - 4 - oxo - 6 - *trans* - methyl - HPI
2 - (cyclohexene - 4 - carbonyl) - 4 - oxo - 7 - methyl - HPI
2 - (cyclohexene - 4 - carbonyl) - 4 - oxo - 8 - methyl - HPI
2 - (cyclohexene - 4 - carbonyl) - 4 - oxo - 9 - methyl - HPI
2 - (cyclohexene - 4 - carbonyl) - 4 - oxo - 10 - methyl - HPI
2 - (cyclohexene - 4 - carbonyl) - 4 - oxo - 11 - methyl - HPI
2 - (cyclohexene - 4 - carbonyl) - 4 - oxo - 11*b* - methyl - HPI

d) 1 ml. phosphorus trichloride is added dropwise at 140°C. to a solution of 6.5 g. 4 - oxo - 6 - *trans* - methyl - HPI and 5 g. 3 - nitrobenzoic acid in 50 ml. chlorobenzene. The reaction mixture is boiled for an hour, then evaporated and the residue chromatographed over silica gel with chloroform as elution agent to give 2 - (3 - nitrobenzoyl) - 4 - oxo - 6 - *trans* - methyl - HPI, which melts at 90—92°C.

The following compounds are obtained analogously by acylation of the appropriate compounds:

1 - methyl - 2 - nicotinoyl - 4 - oxo - HPI
2 - nicotinoyl - 3 - methyl - 4 - oxo - HPI
2 - nicotinoyl - 4 - oxo - 6 - *cis* - methyl - HPI
2 - nicotinoyl - 4 - oxo - 6 - *trans* - methyl - HPI
2 - nicotinoyl - 4 - oxo - 7 - methyl - HPI
2 - nicotinoyl - 4 - oxo - 8 - methyl - HPI
2 - nicotinoyl - 4 - oxo - 9 - methyl - HPI
2 - nicotinoyl - 4 - oxo - 10 - methyl - HPI
2 - nicotinoyl - 4 - oxo - 11 - methyl - HPI
2 - nicotinoyl - 4 - oxo - 11*b* - methyl - HPI
1 - methyl - 2 - (2 - thienylcarbonyl) - 4 - oxo - HPI
2 - (2 - thienylcarbonyl) - 3 - methyl - 4 - oxo - HPI
2 - (2 - thienylcarbonyl) - 4 - oxo - 6 - *cis* - methyl - HPI
2 - (2 - thienylcarbonyl) - 4 - oxo - 6 - *trans* - methyl - HPI
2 - (2 - thienylcarbonyl) - 4 - oxo - 7 - methyl - HPI
2 - (2 - thienylcarbonyl) - 4 - oxo - 8 - methyl - HPI
2 - (2 - thienylcarbonyl) - 4 - oxo - 9 - methyl - HPI
2 - (2 - thienylcarbonyl) - 4 - oxo - 10 - methyl - HPI
2 - (2 - thienylcarbonyl) - 4 - oxo - 11 - methyl - HPI
2 - (2 - thienylcarbonyl) - 4 - oxo - 11*b* - methyl - HPI
1 - methyl - 2 - (3 - thienylcarbonyl) - 4 - oxo - HPI
2 - (3 - thienylcarbonyl) - 3 - methyl - 4 - oxo - HPI
2 - (3 - thienylcarbonyl) - 4 - oxo - 6 - *cis* - methyl - HPI
2 - (3 - thienylcarbonyl) - 4 - oxo - 6 - *trans* - methyl - HPI
2 - (3 - thienylcarbonyl) - 4 - oxo - 7 - methyl - HPI
2 - (3 - thienylcarbonyl) - 4 - oxo - 8 - methyl - HPI
2 - (3 - thienylcarbonyl) - 4 - oxo - 9 - methyl - HPI
2 - (3 - thienylcarbonyl) - 4 - oxo - 10 - methyl - HPI
2 - (3 - thienylcarbonyl) - 4 - oxo - 11 - methyl - HPI
2 - (3 - thienylcarbonyl) - 4 - oxo - 11*b* - methyl - HPI

e) A solution of 6.5 g. 4 - oxo - 6 - *cis* - methyl - HPI, 4.8 g. isobutyric acid anhydride and 2.2 g. triethylamine in 100 ml. dichloromethane is left to stand overnight at 20°C., whereafter the reaction mixture is worked up as usual to give 2 - isobutyryl - 4 - oxo - 6 - *cis* - methyl - HPI, which melts at 136°C.

f) 5 g. 4 - oxo - 6 - *cis* - methyl - HPI, 4 g. 3 - nitrobenzoic acid and 3 g. silicon tetrachloride in 100 ml. pyridine are boiled for an hour, then poured on to ice and worked up as usual to give 2 - (3 - nitrobenzoyl) - 4 - oxo - 6 - *cis* - methyl - HPI, which melts at 184—185°C.

g) 3.3 g. (2 - cyclohexene - 4 - carbonyl) - 4 - oxo - 6 - *trans* - methyl - HPI in 100 ml. tetrahydrofuran are hydrogenated on 0.3 g. platinum oxide at 20°C. and at atmospheric pressure, whereafter the solvent is distilled off to give 2 - cyclohexylcarbonyl - 4 - oxo - 6 - *trans* - methyl - HPI, which melts at 134°C.

Example 3

Crude 1 - (N - benzoyl - N - carboxymethylaminomethyl) - 4 - methyl - 1,2,3,4 - tetrahydroisoquinoline, obtained by the reaction of 1.4 g. 2 - phenylpropylamine with 2.7 g. N - (2,2 - dimethoxyethyl) - N - carboxymethylbenzamide (obtainable by the reaction of trimethylsilyl hippurate with tri-

methylsilyl chloride/triethylamine and chloroacetaldehyde dimethyl acetal) in 20 ml. concentrated hydrochloride at 70°C., is boiled overnight with toluene for the removal of water. Upon cooling, 2 - benzoyl - 4 - oxo - 7 - methyl - HPI crystallises out. It melts at 157°C.

In an analogous manner, from 1 - (N - benzoyl - N - carboxymethylaminoethyl) - 4 - phenyl - 1,2,3,4 - tetrahydroisoquinoline (obtainable from 2,2 - diphenylethylamine), there is obtained 2 - benzoyl - 4 - oxo - 7 - phenyl - HPI.

Example 4

3.4 g. 1 - benzoyl - 3 - oxo - 4 - (2 - hydroxyethyl) - 5 - *p* - tolylpiperazine (obtainable by the reaction of *p* - tolylglyoxal bisulphite adduct with aminomalondiamide to give 2 - aminocarbonyl - 3 - hydroxy - 5 - *p* - tolylpyrazine, saponification and decarboxylation to 3 - hydroxy - 5 - *p* - tolylpyrazine, hydrogenation to 3 - oxo - 5 - *p* - tolylpiperazine, reaction with benzoyl chloride to give 1 - benzoyl - 3 - oxo - 5 - *p* - tolylpiperazine and reaction with ethylene oxide in the presence of sodium hydroxide) in about 50 ml. liquid hydrogen fluoride is left to stand for 3 days at 20°C., whereafter the reaction mixture is poured into ice water and then worked up as usual to give 2 - benzoyl - 4 - oxo - 9 - methyl - HPI, which has a melting point of 162—163°C.

Example 5

3.6 g. 1 - benzoyl - 3 - oxo - 4 - (2 - chloroethyl) 5 - *p* - tolylpiperazine (obtainable from 1 - benzoyl - 3 - oxo - 4 - (2 - hydroxyethyl) - 5 - *p* - tolylpiperazine by reaction with thionyl chloride) in 50 ml. carbon disulphide are added, with ice cooling, to 0.5 g. aluminium trichloride in 50 ml. carbon disulphide. The reaction mixture is stirred for 12 hours, then poured on to ice and worked up as usual to give 2 - benzoyl - 4 - oxo - 9 - methyl - HPI, which melts at 162—163°C.

Example 6

a) 3.37 g. 1 - benzoyl - 3 - oxo - 5 - phenyl - piperazinyl - 4 - acetic acid are dissolved in 15 ml. liquid hydrogen fluoride, whereafter the solution is left to stand for 2 days, then poured on to ice. After the usual working up, there is obtained 2 - benzoyl - 4,7 - dioxo - HPI.

b) 3.2 g. 2 - benzoyl - 4,7 - dioxo - HPI are dissolved in 60 ml. methanol, 0.5 g. sodium borohydride is added thereto portionwise at 0°C. and the reaction mixture is stirred for 12 hours at 20°C. and poured on to ice. There is thus obtained 2 - benzoyl - 4 - oxo - 7 - hydroxy - HPI.

c) 3.22 g. 2 - benzoyl - 4 - oxo - 7 - hydroxy - HPI are dissolved in 20 ml. chloroform and subsequently 1.3 g. thionyl chloride in 5 ml. chloroform added thereto dropwise, while stirring. The reaction mixture is boiled for an hour, then evaporated and, after the usual working up, there is obtained 2 - benzoyl - 4 - oxo - 7 - chloro - HPI.

Example 7

a) 3.70 g. 1 - benzoyl - 3 - oxo - 4 - chlorocarbonylmethyl - 5 - *p* - tolyl - piperazine are dissolved in 50 ml. nitrobenzene, 1.4 g. aluminium trichloride are added thereto and the reaction mixture is stirred overnight at 20°C., whereafter, after the usual working up, there is obtained 2 - benzoyl - 4,7 - dioxo - 9 - methyl - HPI.

b) 3.34 g. 2 - benzoyl - 4,7 - dioxo - 9 - methyl - HPI, 1.5 g. potassium hydroxide, 3 ml. 35% hydrazine and 25 ml. diethylene glycol are heated to 100°C. for an hour and the temperature is then slowly increased until the hydrazone formed is destroyed, whereby excess hydrazine and water evaporate off, whereafter the reaction mixture is boiled for 4 hours. The reaction mixture is then cooled and, after the usual working up, there is obtained 2 - benzoyl - 4 - oxo - 9 - methyl - HPI, which melts at 162—163°C.

c) 3.6 g. 2 - benzoyl - 4 - oxo - 7 - chloro - 9 - methyl - HPI (obtainable by the hydrogenation of 2 - benzoyl - 4,7 - dioxo - 9 - methyl - HPI in the presence of Raney nickel to give 2 - benzoyl - 4 - oxo - 7 - hydroxy - 9 - methyl - HPI and subsequent reaction with thionyl chloride) are hydrogenated in 100 ml. methanol in the presence of 0.3 g. palladium charcoal at 20°C. and at atmospheric pressure, whereafter the solution is concentrated. After the addition of diethyl ether, there is obtained 2 - benzoyl - 4 - oxo - 9 - methyl - HPI, which melts at 162—163°C.

Example 8

3.2 g. 2 - benzoyl - 4 - oxo - 9 - methyl - 2,3,6,7 - tetrahydro - 4H - pyrazino[2,1 - a]-isoquinoline (obtainable by the cyclisation of 1 - (2 - *m* - tolylethyl) - 4 - benzoyl - piperazine - 2,6 - dione with polyphosphoric acid) are hydrogenated in 200 ml. methanol in the presence of 1.5 g. Raney nickel at 20°C. and at atmospheric pressure. After evaporation of the solvent, there is obtained 2 - benzoyl - 4 - oxo - 9 - methyl - HPI, which melts at 162—163°C.

Example 9

3.2 g. 2 - benzoyl - 4 - oxo - 7 - methylene - HPI (obtainable from 3 - hydroxy - 5 - phenyl - pyrazine by hydrogenation to give 3 - oxo - 5 - phenyl - piperazine, reaction with benzoyl chloride to

give 1 - benzoyl - 3 - oxo - 5 - phenyl - piperazine, reaction with trimethylsilyl chloride/triethylamine and trimethylsilyl chloroacetate to give 1 - benzoyl - 3 - oxo - 5 - phenyl - piperazinyl - 4 - acetic acid, cyclisation with hydrogen fluoride to give 2 - benzoyl - 4,7 - dioxo - HPI and reaction with methylene triphenyl phosphorane in diethyl ether) are hydrogenated in 100 ml. ethanol in the presence of 1 g. 5% palladium charcoal at 40°C. and at atmospheric pressure and then filtered and the filtrate evaporated to give 2 - benzoyl - 4 - oxo - 7 - methyl - HPI, which melts at 157°C.

Example 10

3.2 g. 2 - benzoyl - 4 - oxo - 9 - methyl - 1,2,3,11*b* - tetrahydro - 4H - pyrazino-[2,1 - a]isoquinoline (obtainable from 1 - benzoyl - 3 - oxo - 5 - *p* - tolyl - piperazine by reaction with trimethylsilyl chloride/triethylamine and trimethylsilyl chloroacetate to give 1 - benzoyl - 3 - oxo - 4 - carboxymethyl - 5 - *p* - tolyl - piperazine, reaction with liquid hydrogen fluoride to give 2 - benzoyl - 4,7 - dioxo - 9 - methyl - HPI and reaction with trimethylsilyl chloride/zinc in diethyl ether) are hydrogenated in 50 ml. tetrahydrofuran in the presence of 200 mg. platinum oxide at 20°C. and at atmospheric pressure, followed by filtration and evaporation of the filtrate to give 2 - benzoyl - 4 - oxo - 9 - methyl - HPI, which melts at 162—163°C.

Example 11

5.7 g. 3 - chloroperbenzoic acid are added portionwise to 4.6 g. 2 - (pyridyl - 2 - carbonyl) - 4 - oxo - HPI in 270 ml. dichloromethane and the reaction mixture then left to stand for 24 hours at 20°C. Ammonia is then passed in, the reaction mixture is filtered with suction and the solvent is evaporated off from the filtrate to give 1 - hydroxy - 2 - (pyridyl - 2 - carbonyl) - 4 - oxo - HPI which, after recrystallisation from acetone, melts at 140°C.

Example 12

76.5 g. 2 - benzoyl - 4 - oxo - HPI in 1 litre anhydrous tetrahydrofuran are added dropwise to a suspension of sodamide, prepared from 5.75 g. sodium in 1250 ml. liquid ammonia, whereafter the reaction mixture is stirred for an hour, 32 ml. ethylene oxide are added thereto and the reaction mixture is stirred overnight. It is then allowed to come to ambient temperature and the solvent is distilled off. After the usual working up, there is obtained a resin which is chromatographically purified over silica gel, using chloroform as elution agent. There is obtained 2 - benzoyl - 3 - (2 - hydroxyethyl) - 4 - oxo - HPI which, after recrystallisation from ethyl acetate/diethyl ether, melts at 194°C.

Example 13

3.12 g. 2 - cyclohexylcarbonyl - 4 - oxo - HPI are dissolved in 50 ml. chloroform, a solution of 1.6 g. bromine in 20 ml. chloroform is added dropwise thereof, while stirring, at 20°C. and the reaction mixture is stirred overnight. After the usual working up, there is obtained 2 - cyclohexylcarbonyl - 4 - oxo - 8(?) - bromo - HPI (the position of the bromine atom is not definite). Other bromination products are thereby also formed.

Example 14

a) A solution of 31.2 g. 2 - cyclohexylcarbonyl - 4 - oxo - HPI in 50 ml. acetic acid is added at 10°C. to 100 g. of fuming sulphuric acid (30% by weight of sulphur trioxide), cooled to 0°C. and 5 ml. nitric acid (D=1.52) in 10 ml. acetic acid added dropwise thereto at a temperature below 20°C. The reaction mixture is stirred for an hour at 10—20°C., hydrolysed with ice water and extracted with chloroform. The chloroform extract is purified chromatographically on silica gel, using ethyl acetate as elution agent. There is obtained 2 - cyclohexylcarbonyl - 4 - oxo - 11(or 8) - nitro - HPI (R_f value about 0.4) and 2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - nitro - HPI (R_f value 0.25). Both compounds exhibit infra-red bands at 1660, 1530, 1350 and 750 cm^{-1} and mass peaks at m/e=246; 357.

The following compounds are obtained analogously by the nitration of the corresponding compounds which are unsubstituted in the 8- and 11-positions:

1 - methyl - 2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - nitro - HPI
1 - methyl - 2 - cyclohexylcarbonyl - 4 - oxo - 11(or 8) - nitro - HPI
2 - cyclohexylcarbonyl - 3 - methyl - 4 - oxo - 8(or 11) - nitro - HPI
2 - cyclohexylcarbonyl - 3 - methyl - 4 - oxo - 11(or 8) - nitro - HPI
2 - cyclohexylcarbonyl - 4 - oxo - 6 - *cis* - methyl - 8(or 11) - nitro - HPI
2 - cyclohexylcarbonyl - 4 - oxo - 6 - *cis* - methyl - 11(or 8) - nitro - HPI
2 - cyclohexylcarbonyl - 4 - oxo - 6 - *trans* - methyl - 8(or 11) - nitro - HPI
2 - cyclohexylcarbonyl - 4 - oxo - 6 - *trans* - methyl - 11(or 8) - nitro - HPI
2 - cyclohexylcarbonyl - 4 - oxo - 7 - methyl - 8(or 11) - nitro - HPI
2 - cyclohexylcarbonyl - 4 - oxo - 7 - methyl - 11(or 8) - nitro - HPI
2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - nitro - 9 - methyl - HPI
2 - cyclohexylcarbonyl - 4 - oxo - 9 - methyl - 11(or 8) - nitro - HPI
2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - nitro - 10 - methyl - HPI

2 - cyclohexylcarbonyl - 4 - oxo - 10 - methyl - 11(or 8) - nitro - HPI

2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - nitro - 11*b* - methyl - HPI

2 - cyclohexylcarbonyl - 4 - oxo - 11(or 8) - nitro - 11*b* - methyl - HPI

1 - methyl - 2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - 8(or 11) - nitro - HPI

1 - methyl - 2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - 11(or 8) - nitro - HPI

2 - (tetrahydropyranyl - 4 - carbonyl) - 3 - methyl - 4 - oxo - 8(or 11) - nitro - HPI

2 - (tetrahydropyranyl - 4 - carbonyl) - 3 - methyl - 4 - oxo - 11(or 8) - nitro - HPI

2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - 6 - *cis* - methyl - 8(or 11) - nitro - HPI

2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - 6 - *cis* - methyl - 11(or 8) - nitro - HPI

2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - 6 - *trans* - methyl - 8(or 11) - nitro - HPI

2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - 6 - *trans* - methyl - 11(or 8) - nitro - HPI

2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - 7 - methyl - 8(or 11) - nitro - HPI

2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - 7 - methyl - 11(or 8) - nitro - HPI

2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - 8(or 11) - nitro - 9 - methyl - HPI

2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - 9 - methyl - 11(or 8) - nitro - HPI

2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - 8(or 11) - nitro - 10 - methyl - HPI

2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - 10 - methyl - 11(or 8) - nitro - HPI

2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - 8(or 11) - nitro - 11*b* - methyl - HPI

2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - 11(or 8) - nitro - 11*b* - methyl - HPI

1 - methyl - 2 - (thiacyclohexyl - 4 - carbonyl) - 4 - oxo - 8(or 11) - nitro - HPI

1 - methyl - 2 - (thiacyclohexyl - 4 - carbonyl) - 4 - oxo - 11(or 8) - nitro - HPI

2 - (thiacyclohexyl - 4 - carbonyl) - 3 - methyl - 4 - oxo - 8(r 11) - nitro - HPI

2 - (thiacyclohexyl - 4 - carbonyl) - 3 - methyl - 4 - oxo - 11(or 8) - nitro - HPI

2 - (thiacyclohexyl - 4 - carbonyl) - 4 - oxo - 6 - *cis* - methyl - 8(or 11) - nitro - HPI

2 - (thiacyclohexyl - 4 - carbonyl) - 4 - oxo - 6 - *cis* - methyl - 11(or 8) - nitro - HPI

2 - (thiacyclohexyl - 4 - carbonyl) - 4 - oxo - 6 - *trans* - methyl - 8(or 11) - nitro - HPI

2 - (thiacyclohexyl - 4 - carbonyl) - 4 - oxo - 6 - *trans* - methyl - 11(or 8) - nitro - HPI

2 - (thiacyclohexyl - 4 - carbonyl) - 4 - oxo - 7 - methyl - 8(or 11) - nitro - HPI

2 - (thiacyclohexyl - 4 - carbonyl) - 4 - oxo - 7 - methyl - 11(or 8) - nitro - HPI

2 - (thiacyclohexyl - 4 - carbonyl) - 4 - oxo - 8(or 11) - nitro - 9 - methyl - HPI

2 - (thiacyclohexyl - 4 - carbonyl) - 4 - oxo - 9 - methyl - 11(or 8) - nitro - HPI

2 - (thiacyclohexyl - 4 - carbonyl) - 4 - oxo - 8(or 11) - nitro - 10 - methyl - HPI

2 - (thiacyclohexyl - 4 - carbonyl) - 4 - oxo - 10 - methyl - 11(or 8) - nitro - HPI

2 - (thiacyclohexyl - 4 - carbonyl) - 4 - oxo - 8(or 11) - nitro - 11*b* - methyl - HPI

2 - (thiacyclohexyl - 4 - carbonyl) - 4 - oxo - 11(or 8) - nitro - 11*b* - methyl - HPI

2 - benzoyl - 4 - oxo - 8(or 11) - nitro - HPI

2 - benzoyl - 4 - oxo - 11(or 8) - nitro - HPI

2 - (3 - fluorobenzoyl) - 4 - oxo - 8(or 11) - nitro - HPI

2 - (3 - fluorobenzoyl) - 4 - oxo - 11(or 8) - nitro - HPI

2 - (4 - fluorobenzoyl) - 4 - oxo - 8(or 11) - nitro - HPI

2 - (4 - fluorobenzoyl) - 4 - oxo - 11(or 8) - nitro - HPI

2 - (3 - nitrobenzoyl) - 4 - oxo - 8(or 11) - nitro - HPI

2 - (3 - nitrobenzoyl) - 4 - oxo - 11(or 8) - nitro - HPI

2 - (4 - nitrobenzoyl) - 4 - oxo - 8(or 11) - nitro - HPI

2 - (4 - nitrobenzoyl) - 4 - oxo - 11(or 8) - nitro - HPI

b) 4.1 g. 2 - cyclohexylcarbonyl - 4 - oxo - 11(or 8) - nitro - HPI are hydrogenated in 100 ml. methanol in the presence of 2 g. 5% palladium charcoal at 20°C. and at atmospheric pressure. After filtration and evaporation of the solvent, the residue is chromato-

graphed on silica gel, using chloroform/methanol (98:2) as elution agent. There is obtained 2 - cyclohexylcarbonyl - 4 - oxo - 11(or 8) - amino - HPI which, after recrystallisation from benzene/petroleum ether, melts at 160—162°C.

The following compounds are obtained analogously by hydrogenation of the appropriate nitro compounds:

2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - amino - HPI
1 - methyl - 2 - (3 - aminobenzoyl) - 4 - oxo - HPI
2 - (3 - aminobenzoyl) - 3 - methyl - 4 - oxo - HPI
2 - (3 - aminobenzoyl) - 4 - oxo - 6 - *cis* - methyl - HPI hydrochloride; m.p. 195°C.
2 - (3 - aminobenzoyl) - 4 - oxo - 6 - *trans* - methyl - HPI hydrochloride; m.p. 205°C.
2 - (3 - aminobenzoyl) - 4 - oxo - 7 - methyl - HPI
2 - (3 - aminobenzoyl) - 4 - oxo - 8 - methyl - HPI
2 - (3 - aminobenzoyl) - 4 - oxo - 8 - amino - HPI
2 - (3 - aminobenzoyl) - 4 - oxo - 8 - fluoro - HPI
2 - (3 - aminobenzoyl) - 4 - oxo - 8 - chloro - HPI
2 - (3 - aminobenzoyl) - 4 - oxo - 9 - methyl - HPI
2 - (3 - aminobenzoyl) - 4 - oxo - 9 - amino - HPI
2 - (3 - aminobenzoyl) - 4 - oxo - 9 - fluoro - HPI
2 - (3 - aminobenzoyl) - 4 - oxo - 9 - chloro - HPI
2 - (3 - aminobenzoyl) - 4 - oxo - 10 - methyl - HPI
2 - (3 - aminobenzoyl) - 4 - oxo - 10 - amino - HPI
2 - (3 - aminobenzoyl) - 4 - oxo - 10 - fluoro - HPI
2 - (3 - aminobenzoyl) - 4 - oxo - 10 - chloro - HPI
2 - (3 - aminobenzoyl) - 4 - oxo - 11 - methyl - HPI
2 - (3 - aminobenzoyl) - 4 - oxo - 11 - amino - HPI
2 - (3 - aminobenzoyl) - 4 - oxo - 11 - fluoro - HPI
2 - (3 - aminobenzoyl) - 4 - oxo - 11 - chloro - HPI
2 - (3 - aminobenzoyl) - 4 - oxo - 11*b* - methyl - HPI
1 - methyl - 2 - (4 - aminobenzoyl) - 4 - oxo - HPI
2 - (4 - aminobenzoyl) - 3 - methyl - 4 - oxo - HPI
2 - (4 - aminobenzoyl) - 4 - oxo - 6 - *cis* - methyl - HPI, ethanol solvate, m.p. 226°C.
2 - (4 - aminobenzoyl) - 4 - oxo - 6 - *trans* - methyl - HPI
2 - (4 - aminobenzoyl) - 4 - oxo - 7 - methyl - HPI
2 - (4 - aminobenzoyl) - 4 - oxo - 8 - methyl - HPI
2 - (4 - aminobenzoyl) - 4 - oxo - 8 - amino - HPI
2 - (4 - aminobenzoyl) - 4 - oxo - 8 - fluoro - HPI
2 - (4 - aminobenzoyl) - 4 - oxo - 8 - chloro - HPI
2 - (4 - aminobenzoyl) - 4 - oxo - 9 - methyl - HPI
2 - (4 - aminobenzoyl) - 4 - oxo - 9 - amino - HPI
2 - (4 - aminobenzoyl) - 4 - oxo - 9 - fluoro - HPI
2 - (4 - aminobenzoyl) - 4 - oxo - 9 - chloro - HPI
2 - (4 - aminobenzoyl) - 4 - oxo - 10 - methyl - HPI
2 - (4 - aminobenzoyl) - 4 - oxo - 10 - amino - HPI
2 - (4 - aminobenzoyl) - 4 - oxo - 10 - fluoro - HPI
2 - (4 - aminobenzoyl) - 4 - oxo - 10 - chloro - HPI
2 - (4 - aminobenzoyl) - 4 - oxo - 11 - methyl - HPI
2 - (4 - aminobenzoyl) - 4 - oxo - 11 - amino - HPI
2 - (4 - aminobenzoyl) - 4 - oxo - 11 - fluoro - HPI
2 - (4 - aminobenzoyl) - 4 - oxo - 11 - chloro - HPI
2 - (4 - aminobenzoyl) - 4 - oxo - 11*b* - methyl - HPI
2 - (3 - aminobenzoyl) - 4 - thioxo - HPI
2 - (4 - aminobenzoyl) - 4 - thioxo - HPI

c) A solution of 4.9 g. 2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - amino - HPI and 1.5 g. 33% formaldehyde solution in 200 ml. methanol is hydrogenated in the presence of 1 g. 5% palladium charcoal at 20°C. and at atmospheric pressure. Subsequently, the reaction mixture is filtered and evaporated and the residue is purified by chromatographing over silica gel, using chloroform as elution agent. There is obtained 2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - methyl - amino - HPI.

The following compounds are obtained analogously from the appropriate primary amines:

2 - cyclohexylcarbonyl - 4 - oxo - 11(or 8) - methylamino - HPI
2 - (3 - methylaminobenzoyl) - 4 - oxo - 6 - *cis* - methyl - HPI
2 - (3 - methylaminobenzoyl) - 4 - oxo - 6 - *trans* - methyl - HPI

2 - (4 - methylaminobenzoyl) - 4 - oxo - 6 - *cis* - methyl - HPI
2 - (4 - methylaminobenzoyl) - 4 - thioxo - HPI
2 - (4 - *n* - butylaminobenzoyl) - 4 - thioxo - HPI

d) In a manner analogous to that described in c) above, from 4.9 g. 2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - amino - HPI and 4 g. 33% formaldehyde solution, there is obtained 2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - dimethylamino - HPI.

The following compounds are obtained analogously from the corresponding primary or secondary amines:

2 - cyclohexylcarbonyl - 4 - oxo - 11(or 8) - dimethylamino - HPI
2 - (3 - dimethylaminobenzoyl) - 4 - oxo - 6 - *cis* - methyl - HPI
2 - (3 - dimethylaminobenzoyl) - 4 - oxo - 6 - *trans* - methyl - HPI
2 - (4 - dimethylaminobenzoyl) - 4 - oxo - 6 - *cis* - methyl - HPI

e) Within the course of 2 hours, 3.3 g. 2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - amino - HPI in 100 ml. dioxan are mixed with 2.5 g. dimethyl sulphate and the reaction mixture subsequently stirred at 100°C. for 15 hours. 1.4 g. potassium hydroxide in 5 ml. water are then stirred into the cooled solution. After the usual working up, there is obtained 2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - dimethylamino - HPI.

In an analogous manner, with the use of diethyl sulphate and *n* - butyl bromide, there are obtained the following compounds:

2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - diethylamino - HPI
2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - di - *n* - butylamino - HPI

f) 4.2 g. 2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - trifluoroacetamido - HPI (preparable by the reaction of 2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - amino - HPI with trifluoroacetic anhydride/triethylamine in dichloromethane) are heated with 11.4 g. methyl iodide in 100 ml. dry acetone almost to boilng. 4.5 g. pulverised potassium hydroxide are then added thereto, followed by heating to the boil for 5 minutes, whereafter the reaction mixture is evaporated, the residue is mixed with water, stirred for 2 hours at 20°C. and then worked up as usual to give 2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - methylamino - HPI.

If the methyl iodide is not removed before the hydrolysis, then there is obtained 2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - dimethylamino - HPI.

g) 9.8 g. 2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - amino - HPI and 1.5 g. formic acid in 100 ml. toluene are heated for 5 hours, with a water separator, then evaporated to dryness and, after trituration of the residue with diethyl ether, there is obtained 2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - formamido - HPI.

h) 2.4 g. acetyl chloride in 50 ml. chloroform are added to 9.8 g. 2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - amino - HPI and 3.1 g. triethylamine in 300 ml. chloroform and the reaction mixture is heated for 3 hours and then worked up as usual to give 2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - acetamido - HPI.

The following compounds are obtained in an analogous manner with propionyl chloride and butyryl chloride:

2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - propionamido - HPI
2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - butyramido - HPI

i) The diazonium fluoroborate prepared from 3.3 g. 2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - amino - HPI, 8 ml. 35% tetrafluoroboric acid, 0.7 g. sodium nitrite and 4 ml. water is filtered off, washed with 5% tetrafluoroboric acid, with a little ethanol and with diethyl ether, dried and decomposed at 130—150°C. There is obtained 2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - fluoro - HPI. Mass spectrum: m/e=219; 330.

j) The aqueous suspension of the diazonium fluoroborate obtained according to i) above is irradiated with a high pressure mercury lamp until the evolution of gas is finished. The reaction mixture is then extracted with chloroform and again there is obtained 2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - fluoro - HPI.

k) 2.5 g. 2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - amino - HPI are diazotised in 3 ml. 25% hydrochloric acid at about 0—5°C. with a solution of 0.52 g. sodium nitrite in 3 ml. water. The diazonium solution is added dropwise, with stirring, to a mixture of 1 g. cuprous chloride with 4 ml. concentrated hydrochloric acid. The reaction mixture is slowly heated to about 90°C. until the evolution of gas has finished, followed by cooling, extraction with chloroform and purification of the organic phase chromatographically on silica gel to give 2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - chloro - HPI; mass spectrum: m/e=235; 346.

l) A diazonium solution prepared from 3.3 g. 2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - amino - HPI, 1.4 ml. concentrated

sulphuric acid, 5 ml. water and 0.87 g. sodium nitrite is added, with stirring, to a solution of 4 g. potassium cyanide and 3.4 g. copper sulphate in 40 ml. water, buffered with 3.5 g. sodium bicarbonate. The reaction mixture is left to stand for half an hour and then worked up as usual to give 2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - cyano - HPI; mass spectrum: m/e=226; 337.

m) 2.5 g. 2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - amino - HPI are dissolved in 3 ml. 25% hydrochloric acid and a solution of 0.52 g. sodium nitrite in 3 ml. water added thereto. The diazonium salt solution is introduced, with stirring, into 50 ml. boiling water. Subsequently, it is boiled for 30 minutes and then worked up as usual to give 2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - hydroxy - HPI.

The following compounds are obtained in an analogous manner:

2 - cyclohexylcarbonyl - 4 - oxo - 11(or 8) - hydroxy - HPI
2 - (3 - hydroxybenzoyl) - 4 - oxo - 6 - *cis* - methyl - HPI
2 - (3 - hydroxybenzoyl) - 4 - oxo - 6 - *trans* - methyl - HPI
2 - (4 - hydroxybenzoyl) - 4 - oxo - 6 - *cis* - methyl - HPI

n) A diazonium salt solution prepared from 3.3 g. 2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - amino - HPI, 5 ml. 6N hydrochloric acid, 0.7 g. sodium nitrite and 4 ml. water is allowed to run into a solution of 1.4 g. salicylic acid in 15 ml. 2N aqueous sodium hydroxide solution at 5—10°C. After 30 minutes, the product obtained is precipitated out with hydrochloric acid, filtered off, washed with water and a little ethanol and dried. There is obtained orange-red 2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - (3 - carboxy - 4 - hydroxyphenylazo) - HPI.

The following compounds are obtained in an analogous manner with dimethylaniline, 2 - naphthol - 6 - sulphonic acid and 2 - methylanisole:

2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - (4 - dimethylaminophenylazo) - HPI
2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - (2 - hydroxy - 6 - sulpho - 1 - naphthylazo) - HPI
2 - cyclohexylcarbonyl - 4 - oxo - 8(or 11) - 3 - methyl - 4 - methoxyphenylazo - HPI

The following compounds are also obtained in an analogous manner from diazotised 2 - (3 - aminobenzoyl) - 4 - oxo - 6 - *trans* - methyl - HPI with phenol or methylaniline:

2 - (3 - *p* - hydroxyphenylazobenzoyl) - 4 - oxo - 6 - *trans* - methyl - HPI
2 - (3 - *p* - methylaminophenylazobenzoyl) - 4 - oxo - 6 - *trans* - methyl - HPI

Example 15

a) 20.2 g. 4 - oxo - HPI in 500 ml. dioxan are heated to the boil and 20 g. phosphorus pentasulphide are added thereto portionwise within the course of 2 hours. The reaction mixture is heated for a further hour, the solvent is then removed and the residue is worked up as usual. The residue obtained is purified chromatographically over silica gel, using chloroform/methanol (95:5) as elution agent. There is obtained 4 - thioxo - HPI which, after recrystallisation from benzene, melts at 151°C.

In an analogous manner, with excess phosphorus pentasulphide, there is obtained from 2 - cyclohexylcarbonyl - 4 - oxo - HPI, 2 - cyclohexylthiocarbonyl - 4 - thioxo - HPI and from 2 - benzoyl - 4 - oxo - HPI, 2 - thiobenzoyl - 4 - thioxo - HPI.

b) 1.6 g. benzoyl chloride in 50 ml. chloroform are added to a solution of 2.2 g. 4 - thioxo - HPI and 1.1 g. triethylamine in 100 ml. chloroform and the reaction mixture is stirred for an hour at 20°C. After the usual working up, there is obtained 2 - benzoyl - 4 - thioxo - HPI which, after recrystallisation from ethanol, melts at 184°C.

The following compounds are obtained analogously with the use of the appropriate acid chlorides:—

2 - acetyl - 4 - thioxo - HPI
2 - cyclopentylcarbonyl - 4 - thioxo - HPI
2 - cyclohexylcarbonyl - 4 - thioxo - HPI
2 - cycloheptylcarbonyl - 4 - thioxo - HPI
2 - (4 - oxo - cyclohexyl - carbonyl) - 4 - thioxo - HPI
2 - (tetrahydropyranyl - 4 - carbonyl) - 4 - thioxo - HPI
2 - (tetrahydrothiopyranyl - 4 - carbonyl) - 4 - thioxo - HPI
2 - (1 - oxo - 1 - thiacyclohexyl - 4 - carbonyl) - 4 - thioxo - HPI
2 - (1,1 - dioxo - 1 - thiacyclohexyl - 4 - carbonyl) - 4 - thioxo - HPI
2 - (3 - fluorobenzoyl) - 4 - thioxo - HPI
2 - (4 - fluorobenzoyl) - 4 - thioxo - HPI
2 - (3 - chlorobenzoyl) - 4 - thioxo - HPI
2 - (4 - chlorobenzoyl) - 4 - thioxo - HPI
2 - (3 - nitrobenzoyl) - 4 - thioxo - HPI
2 - (4 - nitrobenzoyl) - 4 - thioxo - HPI
2 - (4 - dimethylaminobenzoyl) - 4 - thioxo - HPI

2 - (4 - di - *n* - butylaminobenzoyl) - 4 - thioxo - HPI
2 - (4 - formamidobenzoyl) - 4 - thioxo - HPI
2 - (4 - butyramidobenzoyl) - 4 - thioxo - HPI
2 - (2 - thienylcarbonyl) - 4 - thioxo - HPI
2 - (3 - thienylcarbonyl) - 4 - thioxo - HPI
2 - (2 - pyridylcarbonyl) - 4 - thioxo - HPI
2 - nicotinoyl - 4 - thioxo - HPI
2 - isonicotinoyl - 4 - thioxo - HPI

Example 16

6.4 g. S - thiobenzoyl - mercaptoacetic acid in 15 ml. 2N aqueous sodium hydroxide solution is added to 6.06 g. 4 - oxo - HPI in 150 ml. tetrahydrofuran and the reaction mixture stirred for 12 hours at 20°C. The reaction mixture is worked up as usual to give 2 - thiobenzoyl - 4 - oxo - HPI which, after recrystallisation from ethanol/petroleum ether, melts at 98—99°C.

The following compounds are obtained in an analogous manner by the thioacylation of the appropriate compounds which are unsubstituted in the 2-position:

(+) - 2 - thiobenzoyl - 4 - oxo - HPI; m.p. 167—168°C.; $[\alpha]_D^{20} = +56.1°$
1 - methyl - 2 - thiobenzoyl - 4 - oxo - HPI
2 - thiobenzoyl - 3 - methyl - 4 - oxo - HPI
2 - thiobenzoyl - 4 - thioxo - HPI
2 - thiobenzoyl - 4 - oxo - 6 - *cis* - methyl - HPI; m.p. 100—101°C.
2 - thiobenzoyl - 4 - oxo - 6 - *trans* - methyl - HPI
2 - thiobenzoyl - 4 - oxo - 7 - methyl - HPI
2 - thiobenzoyl - 4 - oxo - 8 - methyl - HPI
2 - thiobenzoyl - 4 - oxo - 9 - methyl - HPI
2 - thiobenzoyl - 4 - oxo - 10 - methyl - HPI
2 - thiobenzoyl - 4 - oxo - 11 - methyl - HPI
2 - thiobenzoyl - 4 - oxo - 11*b* - methyl - HPI
2 - (3 - fluorothiobenzoyl) - 4 - oxo - HPI
1 - methyl - 2 - (3 - fluorothiobenzoyl) - 4 - oxo - HPI
2 - (3 - fluorothiobenzoyl) - 3 - methyl - 4 - oxo - HPI
2 - (3 - fluorothiobenzoyl) - 4 - thioxo - HPI
2 - (3 - fluorothiobenzoyl) - 4 - oxo - 6 - *cis* - methyl - HPI
2 - (3 - fluorothiobenzoyl) - 4 - oxo - 6 - *trans* - methyl - HPI
2 - (3 - fluorothiobenzoyl) - 4 - oxo - 7 - methyl - HPI
2 - (3 - fluorothiobenzoyl) - 4 - oxo - 8 - methyl - HPI
2 - (3 - fluorothiobenzoyl) - 4 - oxo - 9 - methyl - HPI
2 - (3 - fluorothiobenzoyl) - 4 - oxo - 10 - methyl - HPI
2 - (3 - fluorothiobenzoyl) - 4 - oxo - 11 - methyl - HPI
2 - (3 - fluorothiobenzoyl) - 4 - oxo - 11*b* - methyl - HPI
2 - (4 - fluorothiobenzoyl) - 4 - oxo - HPI
1 - methyl - 2 - (4 - fluorothiobenzoyl) - 4 - oxo - HPI
2 - (4 - fluorothiobenzoyl) - 3 - methyl - 4 - oxo - HPI
2 - (4 - fluorothiobenzoyl) - 4 - thioxo - HPI
2 - (4 - fluorothiobenzoyl) - 4 - oxo - 6 - *cis* - methyl - HPI
2 - (4 - fluorothiobenzoyl) - 4 - oxo - 6 - *trans* - methyl - HPI
2 - (4 - fluorothiobenzoyl) - 4 - oxo - 7 - methyl - HPI
2 - (4 - fluorothiobenzoyl) - 4 - oxo - 8 - methyl - HPI
2 - (4 - fluorothiobenzoyl) - 4 - oxo - 9 - methyl - HPI
2 - (4 - fluorothiobenzoyl) - 4 - oxo - 10 - methyl - HPI
2 - (4 - fluorothiobenzoyl) - 4 - oxo - 11 - methyl - HPI
2 - (4 - fluorothiobenzoyl) - 4 - oxo - 11*b* - methyl - HPI

Example 17

6.06 g. 4 - oxo - HPI and 2.5 g. thioacetamide are heated, while stirring, for 3 hours at 140°C. After the usual working up of the reaction mixture, there is obtained 2 - thioacetyl - 4 - oxo - HPI which, after recrystallisation from ethanol, melts at 133°C.

The following compounds are obtained in an analogous manner from the appropriate thioamides and the appropriate compounds unsubstituted in the 2-position:

2 - cyclohexylthiocarbonyl - 4 - oxo - HPI; m.p. 180—181°C.
2 - cyclohexylthiocarbonyl - 3 - methyl - 4 - oxo - HPI
2 - cyclohexylthiocarbonyl - 4 - oxo - 6 - *cis* - methyl - HPI
2 - cyclohexylthiocarbonyl - 4 - oxo - 6 - *trans* - methyl - HPI
2 - cyclohexylthiocarbonyl - 4 - oxo - 7 - methyl - HPI
2 - cyclohexylthiocarbonyl - 4 - oxo - 8 - methyl - HPI
2 - cyclohexylthiocarbonyl - 4 - oxo - 9 - methyl - HPI
2 - cyclohexylthiocarbonyl - 4 - oxo - 10 - methyl - HPI

2 - cyclohexylthiocarbonyl - 4 - oxo - 11 - methyl - HPI

2 - cyclohexylthiocarbonyl - 4 - oxo - 11*b* - methyl - HPI

2 - (pyridyl - 3 - thiocarbonyl) - 4 - oxo - HPI; m.p. 158°C.

2 - (pyridyl - 3 - thiocarbonyl) - 3 - methyl - 4 - oxo - HPI

2 - (pyridyl - 3 - thiocarbonyl) - 4 - oxo - 6 - *cis* - methyl - HPI

2 - (pyridyl - 3 - thiocarbonyl) - 4 - oxo - 6 - *trans* - methyl - HPI

2 - (pyridyl - 3 - thiocarbonyl) - 4 - oxo - 7 - methyl - HPI

2 - (pyridyl - 3 - thiocarbonyl) - 4 - oxo - 8 - methyl - HPI

2 - (pyridyl - 3 - thiocarbonyl) - 4 - oxo - 9 - methyl - HPI

2 - (pyridyl - 3 - thiocarbonyl) - 4 - oxo - 10 - methyl - HPI

2 - (pyridyl - 3 - thiocarbonyl) - 4 - oxo - 11 - methyl - HPI

2 - (pyridyl - 3 - thiocarbonyl) - 4 - oxo - 11*b* - methyl - HPI

2 - (pyridyl - 4 - thiocarbonyl) - 4 - oxo - HPI; m.p. 190°C.

2 - (pyridyl - 4 - thiocarbonyl) - 3 - methyl - 4 - oxo - HPI

2 - (pyridyl - 4 - thiocarbonyl) - 4 - oxo - 6 - *cis* - methyl - HPI

2 - (pyridyl - 4 - thiocarbonyl) - 4 - oxo - 6 - *trans* - methyl - HPI

2 - (pyridyl - 4 - thiocarbonyl) - 4 - oxo - 7 - methyl - HPI

2 - (pyridyl - 4 - thiocarbonyl) - 4 - oxo - 8 - methyl - HPI

2 - (pyridyl - 4 - thiocarbonyl) - 4 - oxo - 9 - methyl - HPI

2 - (pyridyl - 4 - thiocarbonyl) - 4 - oxo - 10 - methyl - HPI

2 - (pyridyl - 4 - thiocarbonyl) - 4 - oxo - 11 - methyl - HPI

2 - (pyridyl - 4 - thiocarbonyl) - 4 - oxo - 11*b* - methyl - HPI

Example 18

3.7 g. cyclohexyl chloroformate in 20 ml. dichloromethane are added at 20°C. to a solution of 4.10 g. 3 - methyl - 4 - oxo - HPI and 2 g. triethylamine in 80 ml. dichloromethane and the reaction mixture then stirred for an hour at 20°C. After the usual working up, there is obtained 2 - cyclohexylcarbonyl - 3 - methyl - 4 - oxo - HPI.

The following compounds are obtained in an analogous manner, with the use of the appropriate chloroformic acid esters:

2 - ethoxycarbonyl - 3 - methyl - 4 - oxo - HPI

2 - ethoxycarbonyl - 4 - oxo - 6 - *cis* - methyl - HPI

2 - ethoxycarbonyl - 4 - oxo - 6 - *trans* - methyl - HPI

2 - ethoxycarbonyl - 4 - oxo - 7 - methyl - HPI

2 - ethoxycarbonyl - 4 - oxo - 8 - methyl - HPI

2 - ethoxycarbonyl - 4 - oxo - 9 - methyl - HPI

2 - ethoxycarbonyl - 4 - oxo - 10 - methyl - HPI

2 - ethoxycarbonyl - 4 - oxo - 11 - methyl - HPI

2 - ethoxycarbonyl - 4 - oxo - 11*b* - methyl - HPI

2 - cyclohexyloxycarbonyl - 4 - oxo - 6 - *cis* - methyl - HPI

2 - cyclohexyloxycarbonyl - 4 - oxo - 6 - *trans* - methyl - HPI

2 - cyclohexyloxycarbonyl - 4 - oxo - 7 - methyl - HPI

2 - cyclohexyloxycarbonyl - 4 - oxo - 8 - methyl - HPI

2 - cyclohexyloxycarbonyl - 4 - oxo - 9 - methyl - HPI

2 - cyclohexyloxycarbonyl - 4 - oxo - 10 - methyl - HPI

2 - cyclohexyloxycarbonyl - 4 - oxo - 11 - methyl - HPI

2 - cyclohexyloxycarbonyl - 4 - oxo - 11*b* - methyl - HPI

2 - cycloheptyloxycarbonyl - 4 - oxo - HPI

The parasitological action of the new compounds according to the present invention is described in more detail in the following:

Example of use:

Action against *Hymenolepis nana* (in mice), *Hymenolepis microstoma* (in mice) and *Hymenolepis diminuta* (in rats).

Experimental animals which had been infected with *H. nana, H. microstoma* or *H. diminuta* were treated after the expiry of the prepatence of the parasites. The active material used was administered orally or subcutaneously as an aqueous suspension.

The degree of action of the preparation was determined in that, after section of the experimental animal, the remaining worms were counted, in comparison with untreated control animals, from which was calculated the percentage activity.

The compounds set out in the following Table show the indicated effectiveness against the above-mentioned parasites:—

TABLE

Active material	Parasite	Effective minimum dosage in mg./kg (parasite reduction >90%)
2-benzoyl-4-oxo-6-*trans*-methyl-HPI	*H. nana* *H. microstoma* *H. diminuta*	25 50 50
2-benzoyl-4-oxo-6-*cis*-methyl-HPI	*H. nana*	50
2-benzoyl-4-oxo-7-methyl-HPI	*H. nana*	25
2-(4-aminobenzoyl)-4-oxo-6-*cis*-methyl-HPI	*H. nana* *H. microstoma*	50 50
2-(3-nitrobenzoyl)-4-oxo-6-*cis*-methyl-HPI	*H. nana*	50
2-cyclohexylcarbonyl-4-oxo-6-*trans*-methyl-HPI	*H. nana* *H. microstoma* *H. diminuta*	50 50 50
2-cyclohexylcarbonyl-4-oxo-8(or 11)-amino-HPI	*H. nana*	50
2-(cyclohex-3-en-yl-carbonyl)-4-oxo-6-*cis*-methyl-HPI	*H. nana*	50
2-thiobenzoyl-4-oxo-HPI	*H. nana* *H. microstoma* *H. diminuta*	50 50 50
2-(pyridyl-3-thiocarbonyl)-4-oxo-HPI	*H. nana*	50
Quinacrine	*H. diminuta*	>1000
Niclosamide	*H. nana* *H. microstoma*	500 500
Dichlorphen	*H. nana* *H. diminuta*	>1000 500

The active materials of general formula (I) can be worked up to pharmaceutical compositions according to the methods known from the literature, as the following Examples demonstrate:

Example A

Tablets for combating cestodes (adult)

a) Tablets containing 500 mg. 2 - benzoyl - 4 - oxo - 7 - methyl - HPI as active material are prepared by working up a powder mixture which consists of 5 kg. 2 - benzoyl - 4 - oxo - 7 - methyl - HPI, 3 kg. lactose, 1.8 kg. maize starch and 0.2 kg. magnesium stearate.

b) The same mixture can be used for the production of tablets which contain 50, 250 and 1000 mg. 2 - benzoyl - 4 - oxo - 7 - methyl - HPI.

The tablets containing 250 and 500 mg. 2 - benzoyl - 4 - oxo - 7 - methyl - HPI as active material are preferably used for human medicine; all of the above-mentioned tablets can be used for veterinary medicinal purposes.

Example B

Tablets preferable for combating cestode hydatids and Schistosomes

a) Effervescent tablets:
Each tablet contains:

2 - benzoyl - 4 - oxo - 7 - methyl - HPI		1000 mg.
citric acid		800 mg.
sodium carbonate		900 mg.
saccharin		5 mg.
saccharose	ad	4000 mg.

b) Sugared chewing tablets:
Each tablet contains:

2 - benzoyl - 4 - oxo - 7 - methyl HPI		2000 mg.
cellulose		80 mg.
sodium carboxymethylcellulose		40 mg.
colouring and aroma materials		as desired
saccharose	ad	4000 mg.

Example C

Dragees for combating cestodes in human medicine

Each dragee core contains:

2 - benzoyl - 4 - oxo - 7 - methyl - HPI	250 mg.
lactose	150 mg.
maize starch	90 mg.
magnesium stearate	10 mg.

The dragee coating consists of talc, saccharose, titanium dioxide, calcium carbonate, polyvinyl - pyrrolidone, methyl cellulose, glycerol, magnesium oxide and lacquer.

This formulation can also be used for dragees which contain 500 mg. 2 - benzoyl - 4 - oxo - 7 - methyl - HPI as active material.

Example D

Syrup for combating cestodes (human medicine)

The syrup is made by preparing a suspension of:

2 - benzoyl - 4 - oxo - 7 - methyl - HPI	3.5 kg.
distilled water	2 litres
buffer	0.1 litres
glycerol	3 kg.
sorbitol	3 kg.
saccharose	53 kg.
mixture of 60% methyl *p* - hydroxy - benzoate and 40% propyl *p* - hydroxy - benzoate	0.1 kg.
ethanol	12 litres

The mixture is admixed with colouring and aroma materials and made up to 100 litres with distilled water.

Example E

Capsules for combating cestodes and Schistosomes in human and veterinary medicine

Capsules of appropriate size are filled with a mixture of:

2 - benzoyl - 4 - oxo - 7 - methyl - HPI	5000 mg.
talc	250 mg.
magnesium stearate	150 mg.

Capsules containing 1000 mg. and 10,000 mg. of the active material are prepared in the same way.

Example F

Injection liquid for human and veterinary medicinal purposes

For subcutaneous administration in oily or aqueous suspension, 15 mg. ampoules are filled with a solution of 500 mg. 2 - benzoyl - 4 - oxo - 7 - methyl - HPI in 6 ml. water and 4 ml. propylene glycol, with the addition of a solubilising agent. The ampoules are heat-sterilised or are provided with a preservation agent.

Similar ampoules are produced containing 100 mg. 2 - benzoyl - 4 - oxo - 7 - methyl - HPI (for small animals) and 1000 mg. 2 - benzoyl - 4 - oxo - 7 - methyl - HPI (for large animals).

Example G

Pellets

A powder mixture is produced from equal parts by weight of 2 - benzoyl - 4 - oxo - 7 - methyl - HPI and lactose which mixture,

together with sodium carboxymethyl - cellulose, is worked up in the usual manner to give a uniform granulate with an average particle size of 1.5 mm.

Example H

Veterinary medicinal pre-mixture which is suitable, with a feedstuff as carrier, for further mixing to a medicated feed

a) 25% pre-mixture (preferably for larger animals)

25 kg. 2 - benzoyl - 4 - oxo - 7 - methyl - HPI are mixed with 75 kg. fine bran (wheat after millings) and/or lactose.

b) 5% pre-mixture (preferably for smaller animals)

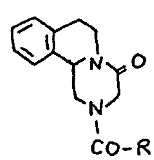
5 kg. 2 - benzoyl - 4 - oxo - 7 - methyl - HPI are worked up in a manner analogous to a) above.

c) Example of a use of the pre-mixture according to a) above for combating *Moniezia* types in bovine intestines.

In order to obtain a suitable medicated feed, 1 kg. of the pre-mixture produced according to a) above is mixed with 9 kg. of a conventional feed concentrate. 400 g. of this medicated feed, containing 10,000 mg. 2 - benzoyl - 4 - oxo - 7 - methyl - HPI are administered for combating *Moniezia* infection in adult cattle.

Analogously to Examples A to H, instead of 2 - benzoyl - 4 - oxo - 7 - methyl - HPI, there can also be used the other active materials for general formula (I) or their physiologically compatible acid-addition salts for the preparation of pharmaceutical compositions.

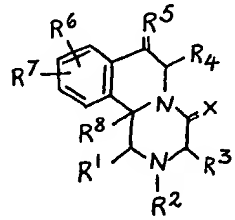
We disclaim compounds of the general formula:—



wherein COR is an acyl radical containing up to 26 carbon atoms derived from an unsubstituted or substituted aliphatic, cycloaliphatic, cycloalkyl aliphatic, aryl aliphatic or heterocyclic carboxylic acid or a substituted aromatic carboxylic acid by removal of the hydroxyl group from the carboxylic radical; and the physiologically compatible salts, the quaternary ammonium salts and the optical antipodes thereof; these compounds being described and claimed in our British Patent Specification No. 1,441,554.

Subject to the above disclaimer
WHAT WE CLAIM IS:—

1. Compounds of the general formula:—



wherein R^1 is a hydrogen atom or a hydroxyl group or an alkyl radical, R^2 is a hydrogen atom or CYR^9, R^3 is a hydrogen atom or an alkyl or hydroxyalkyl radical, R^4 is a hydrogen atom or an alkyl or phenyl radical, R^5 represents two hydrogen atoms or a hydrogen atom and a halogen atom or a hydroxyl group or a phenyl or alkyl radical or R^5 represents an oxygen atom, R^6 and R^7, which can be the same or different, are hydrogen or halogen atoms or hydroxyl, amino, nitro or cyano groups or alkyl, alkoxy, acyloxy, monoalkylamino, dialkylamino or acylamino radicals or Z, R^8 is a hydrogen atom or an alkyl radical, R^9 is a hydrogen atom or an alkyl radical containing up to 6 carbon atoms or a cycloalkyl or cycloalkenyl radical containing 5 to 7 carbon atoms which is either unsubstituted or is substituted by an oxygen atom or is substituted once or twice by R^{10} and/or is interrupted in the ring by oxygen, sulphur, SO or SO_2, or is a phenyl radical which is either unsubstituted or is substituted once or twice by R^{10} or Z, or is a thienyl, pyridyl, phenoxy or R^{11} radical, R^{10} is a fluorine or chlorine atom or a hydroxyl, nitro or amino group or a monoalkylamino, dialkylamino or acylamino radical, R^{11} is an alkoxy radical or a cycloalkoxy radical containing 5 to 7 carbon atoms, X and Y, which can be the same or different, are oxygen or sulphur atoms and Z is phenylazo or naphthylazo radical which is either unsubstituted or substituted by halogen, hydroxyl, alkyl, alkoxy, amino, monoalkylamino, dialkylamino, COOH and/or SO_3H, and wherein the alkyl, hydroxyalkyl, alkoxy and acyl radicals each contain up to 4 carbon atoms, insofar as they are not otherwise defined, and wherein R^2 is CSR^9 or COR^{11} when R^1 and R^3 to R^8 are all hydrogen atoms and X is an oxygen atom; and the physiologically compatible salts thereof.

2. 2 - Benzoyl - 4 - oxo - 6 - *cis* - methyl - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1 - a]isoquinoline.

3. 2 - Isobutyryl - 4 - oxo - 6 - *cis* - methyl - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

4. 2 - Cyclohexylcarbonyl - 4 - oxo - 6 - *trans* - methyl - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

5. 2 - Cyclohexylcarbonyl - 4 - oxo - 11*b* - methyl - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

6. 2 - (4 - Oxo - cyclohexylcarbonyl) - 4 -

oxo - 6 - *trans* - methyl - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

7. 2 - (Tetrahydropyranyl - 4 - carbonyl) - 4 - oxo - 6 - *cis* - methyl - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

8. 2 - Benzoyl - 3 - methyl - 4 - oxo - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1 - a]isoquinoline.

9. 2 - Benzoyl - 4 - oxo - 6 - *trans* - methyl - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

10. 2 - Benzoyl - 4 - oxo - 7 - methyl - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1 - a]isoquinoline.

11. 2 - Benzoyl - 4 - oxo - 9 - methyl - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1 - a]isoquinoline.

12. 2 - Benzoyl - 4 - oxo - 9,10 - dimethoxy - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

13. 2 - (4 - Fluorobenzoyl) - 4 - oxo - 6 - *trans* - methyl - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

14. 2 - Benzoyl - 4 - oxo - 9,10 - dihydroxy - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

15. 2 - (4 - Hydroxycyclohexylcarbonyl) - 4 - oxo - 6 - *cis* - methyl - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

16. 2 - (4 - Hydroxycyclohexylcarbonyl) - 4 - oxo - 6 - *trans* - methyl - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

17. 2 - (4,4 - Difluorocyclohexylcarbonyl) - 4 - oxo - 6 - *trans* - methyl - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

18. 4 - Oxo - 6 - *cis* - methyl - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1 - a]isoquinoline.

19. 4 - Oxo - 6 - *trans* - methyl - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1 - a]isoquinoline.

20. 2 - (4 - Nitrobenzoyl) - 4 - oxo - 6 - *cis* - methyl - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

21. 2 - (3 - Nitrobenzoyl) - 4 - oxo - 6 - *cis* - methyl - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

22. 2 - (3 - Nitrobenzoyl) - 4 - oxo - 6 - *trans* - methyl - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

23. 2 - Benzoyl - 4 - oxo - 7 - phenyl - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1 - a]isoquinoline.

24. 2 - Benzoyl - 4,7 - dioxo - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

25. 2 - Benzoyl - 4 - oxo - 7 - hydroxy - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1 - a]isoquinoline.

26. 2 - Benzoyl - 4 - oxo - 7 - chloro - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1 - a]isoquinoline.

27. 2 - Benzoyl - 4,7 - dioxo - 9 - methyl - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1 - a]isoquinoline.

28. 1 - Hydroxy - 2 - (pyridyl - 2 - carbonyl) - 4 - oxo - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

29. 2 - Benzoyl - 3 - (2 - hydroxy - ethyl) - 4 - oxo - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

30. 2 - Cyclohexylcarbonyl - 4 - oxo - 8(?) - bromo - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

31. 2 - Cyclohexylcarbonyl - 4 - oxo - 11 - nitro - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

32. 2 - Cyclohexylcarbonyl - 4 - oxo - 8 - nitro - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

33. 2 - Cyclohexylcarbonyl - 4 - oxo - 11(or 8) - amino - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

34. 2 - (3 - Aminobenzoyl) - 4 - oxo - 6 - *cis* - methyl - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline hydrochloride.

35. 2 - (3 - Aminobenzoyl) - 4 - oxo - 6 - *trans* - methyl - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline hydrochloride.

36. 2 - (4 - Aminobenzoyl) - 4 - oxo - 6 - *cis* - methyl - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline ethanol solvate.

37. 2 - Cyclohexylcarbonyl - 4 - oxo - 8(or 11) - methylamino - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

38. 2 - Cyclohexylcarbonyl - 4 - oxo - 8(or 11) - dimethylamino - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

39. 2 - Cyclohexylcarbonyl - 4 - oxo - 8(or 11) - formamido - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

40. 2 - Cyclohexylcarbonyl - 4 - oxo - 8(or 11) - acetamido - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

41. 2 - Cyclohexylcarbonyl - 4 - oxo - 8(or 11) - fluoro - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

42. 2 - Cyclohexylcarbonyl - 4 - oxo - 8(or 11) - chloro - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

43. 2 - Cyclohexylcarbonyl - 4 - oxo - 8(or 11) - cyano - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

44. 2 - Cyclohexylcarbonyl - 4 - oxo - 8(or 11) - hydroxy - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

45. 2 - Cyclohexylcarbonyl - 4 - oxo - 8(or 11) - (3 - carboxy - 4 - hydroxyphenylazo) - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

46. 4 - Thioxo - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

47. 2 - Benzoyl - 4 - thioxo - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

48. 2 - Thiobenzoyl - 4 - oxo - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1 - a]isoquinoline.

49. (+) - 2 - Thiobenzoyl - 4 - oxo - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1 - a]isoquinoline.

50. 2 - Thiobenzoyl - 4 - oxo - *cis* - methyl - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

51. 2 - Thioacetyl - 4 - oxo - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

52. 2 - Cyclohexylthiocarbonyl - 4 - oxo - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1 - a]isoquinoline.

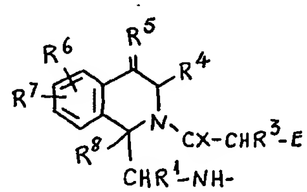
53. 2 - (Pyridyl - 3 - thiocarbonyl) - 4 - oxo - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

54. 2 - (Pyridyl - 4 - thiocarbonyl) - 4 - oxo - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

55. 2 - Benzoyl - 4 - oxo - 11*b* - methyl - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1 - a]isoquinoline.

56. 2 - Cyclohexene - 4 - carbonyl - 4 - oxo - 6 - *cis* - methyl - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline.

57. Process for the preparation of compounds of the general formula given in claim 1, wherein a compound of the general formula Q—R^2, in which Q is a radical of the general formula:—



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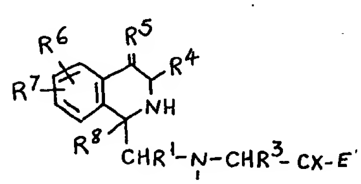

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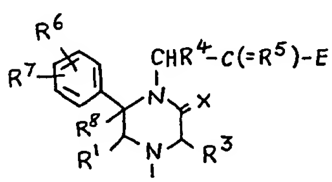
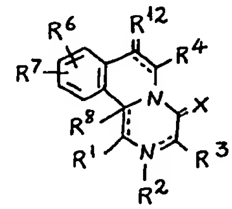


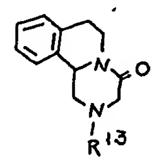
in which E is a hydroxyl group, a functionally changed hydroxyl group or a halogen atom and R^1 to R^8 and X has the same meanings as in claim 1, is cyclised under conditions which split off HE.

58. Process for the preparation of compounds of the general formula given in claim 1, wherein a compound of the general formula:—



wherein R^{12} has the same meaning as R^5 or is an alkylidene radical containing up to 4 carbon atoms and the symbols R^1 to R^8 and X has the same meanings as in claim 1 and the dotted lines indicate that at least in one of these places there can be a double bond, with the proviso that R^{12} is an alkylidene radical when there is no double bond at any of these positions, or a salt thereof, is treated with a reducing agent.

59. Process for the preparation of compounds of the general formula given in claim 1, wherein a compound of the general formula:—



wherein R^{13} is a hydrogen atom or COR^{14}, R^{14} is a hydrogen atom, an alkyl radical containing up to 6 carbon atoms or a cycloalkyl or cycloalkenyl radical containing 5 to 7 carbon atoms which is either unsubstituted or is substituted by oxygen or once or twice by R^{10} and/or interrupted in the ring by oxygen, sulphur, SO or SO_2 or is a phenyl radical which is either unsubstituted or is substituted once or twice by R^{10} or Z or is a thienyl or pyridyl radical and R^{10} and Z have the same meanings as in claim 1, is treated with a hydroxylating, hydroxyalkylating, halogenating or nitrating agent or with an agent giving off sulphur.

60. Process for the preparation of compounds of the general formula given in claim 1, wherein a compound of the general formula given in claim 59, in which R^{13} is a hydrogen atom is reacted with a thioacylating agent or with a compound of the general formula R^{11}—CO—E, in which R^{11} has the same meaning as in claim 1 and E has the same meaning as in claim 57.

61. Process according to any of claims 57 to 60, wherein at least one of the substituents R^1 to R^8 and X in the product obtained is replaced by at least one other substituent R^1 to R^8 and X.

62. Process according to any of claims 57 to 61, wherein optically-active starting materials are used to give optically-active products.

63. Process according to any of claims 57 to 61, wherein racemic starting materials are used and the product obtained is resolved into its optically-active isomers.

64. Process according to any of claims 57 to 63, wherein when the product obtained is a base, it is converted into an acid-addition salt or into a quaternary ammonium salt.

65. Process according to any of claims 57 to 63, wherein, when the product obtained is an acid-addition salt, the free base is liberated therefrom.

66. Process according to any of claims 57 to 63, wherein, when the product obtained is an acid, it is converted into a salt.

67. Process according to any of claims 57 to 63, wherein, when the product obtained is a salt, the free acid is liberated therefrom.

68. Process for the preparation of compounds according to claim 1, substantially as hereinbefore described and exemplified.

69. Compounds according to claim 1, whenever prepared by the process according to any of claims 57 to 68.

70. Anthelmintic, comprising at least one compound according to claim 1, in admixture with a solid, liquid or semi-liquid pharmaceutical diluent or carrier or in admixture with an animal feed or feed concentrate.

71. Anthelmintic according to claim 70 for oral administration, wherein at least one sweetening and/or flavouring agent is additionally present.

72. Anthelmintic according to claim 70 or 71, wherein the liquid or semi-liquid diluent or carrier contains at least one emulsifying and/or dispersing agent.

73. Anthelmintic, comprising at least one compound according to claim 1 in a capsule.

74. Anthelmintic according to any of claims 70 to 73, substantially as hereinbefore described and exemplified.

75. A method of treating helminthiasis in veterinary medicine, which comprises administering at least one compound according to claim 1.

76. A method of treating helminthiasis in veterinary medicine, which comprises administering an anthelmintic according to any of claims 70 to 74.

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